8ª. ESCOLA LATINO-AMERICANA DE VERÃO EM EPILEPSIA
8ª. ESCUELA LATINO-AMERICANA DE VERANO EN EPILEPSIA
8th. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY
(LASSE)

SÃO PAULO, BRASIL 16 A 25 DE FEVEREIRO DE 2014
Centro de Convenções Santa Mônica

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Prof. Dr. Esper A. Cavalheiro

COMISSÃO LATINO AMERICANA DA INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE)
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EPILEPSIA EM DOENÇAS NEURODEGENERATIVAS E ENVELHECIMENTO

A 8ª. Escola Latino-Americana de Verão em Epilepsia (LASSE) é uma atividade da *International League Against Epilepsy* (ILAE) e da Academia Latino Americana de Epilepsia (ALADE) com o apoio da Liga Brasileira de Epilepsia (LBE).

Com início em 2002, as "Escolas de verão em epilepsia", organizadas pela *International League Against Epilepsy* (ILAE) têm se tornado uma referência como experiência didática. Como professores e alunos permanecem em contato bastante próximo por quase duas semanas consecutivas, esse tipo de Escola tem facilitado a integração entre pesquisadores e alunos permitindo uma melhor compreensão das novas descobertas para o beneficio das pessoas com epilepsia. A oitava edição "Escola Latino-Americana de Verão em Epilepsia (LASSE)" realizada em Guarulhos entre 16 a 25 de fevereiro de 2014 aborda o tema Epilepsia em Doenças Neurodegenerativas e Envelhecimento.

Agradecendo aos professores e tutores que de forma tão generosa abandonam seus afazeres e nos oferecem seu tempo damos boas-vindas aos alunos da LASSE-VIII, razão maior do nosso trabalho.

A Comissão Organizadora

ÍNDICE

8TH. LATIN-AMERICAN SUMMER SCHOOL ON EPILEPSY - LASSE VIII

"Epilepsy in neurodegenerative diseases and aging"

16 a 25 February 2014 – São Paulo, Brazil

PROGRAM

21 Feb.

22 Feb.

23 Feb.

24 Feb. – Surgical approach of the epilepsies

25 Feb. – Group presentations

09:00-18:00 Presentations + coffee-breaks + lunch
20:00 Farewell dinner

Peter Wolf (Denmark)

CONCEPT OF FOCAL AND GENERALIZED ICTOGENESIS

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Concept of generalized and focal ictogenesis

Peter Wolf, Denmark

8th LASSE
Guarulhos, February 16-25, 2014

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The historical concepts

- For hundreds of years epilepsy was synonymous with generalized tonic-clonic seizures
- Other seizure types start to be mentioned occasionally in the 18th century but become mostly described during the 19th century
- Beyond mere description, J.H.Jackson (1835-1911) starts to analyse seizure semiology

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Focal seizures

At Queen Square, London, Jackson together with the neurosurgeon Victor Horsley (1857-1916) identified anatomical sites of epileptogenic lesions. June 22, 1886, first operation on semiology alone.

Horsley in his report coined the term "focal" for this kind of seizures

June 22, 1886 birthdate of semiological significance of the clinical presentation, of term focal, and of epilepsy surgery.

New nosological understanding ⇒ therapeutic consequence

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"Generalized"

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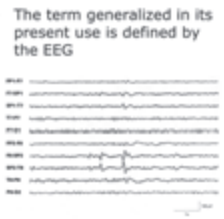
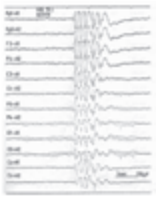
- The term generalized in its present use is defined by the EEG





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Concepts of ictogenesis: 1970 Classification

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- Generalized szs: "Clinical features do not include any sign or symptom referable to an anatomical and/or functional system localized in one hemisphere. … The responsible neuronal discharge takes place, if not throughout the entire grey matter, then at least in the greater part of it and simultaneously on both sides."
- Note: the definition of generalized seizures is negative!

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The concept of generalized epilepsy

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- "Generalized seizures are commonly thought to involve the entire brain homogeneously" (*McNally KA, Blumenfeld H Epilepsy & Behavior 2004; 5:3-12*)
  - How correct is this (EEG – based) common view?

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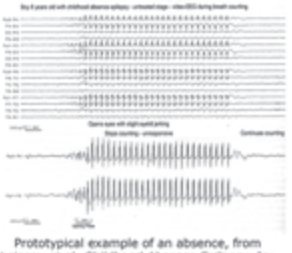
Generalised SW discharges typically are symmetric, synchronous and widespread -

but typically also have a frontal accentuation, especially at onset



Prototypical example of an absence, from Loiseau et al. *Childhood Absence Epilepsy*. In: Roger et al, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*, 2002

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"pseudofocal" discharge

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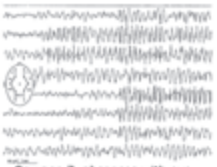
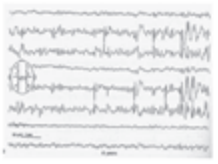


Boy age 7, absences with eye deviation to left. Benign course.



6 year old girl, CAE, untreated
Full response to ethosuximide

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Historical controversy: Spikes and waves a cortical or a subcortical phenomenon?

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Montreal group (Gloor 1969): spike-waves are generated in a thalamo-cortical circuit: Thalamo-cortical concept of generalised ictogenesis

based on animal models and on stimulation (metrazol, amobarbital) of patients

Onset variable

SW a resonance phenomenon

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"Frontal" changes in JME: ^{11}C-FMZ PET

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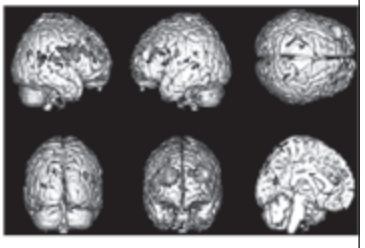
JME:
Global ⇑ of FMZ binding ($GABA_A$ receptors), especially in dorso-lateral pre-frontal cortex -

but also PO



Koepp MJ & Duncan JS. PET in IGE: Imaging beyond structure. In: Juvenile myoclonic epilepsy: The Janz syndrome. Schmitz B, Sander T (Eds). Wrightson, London, 2000: 91-99.

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Absence seizures: Individual patterns revealed by EEG-fMRI

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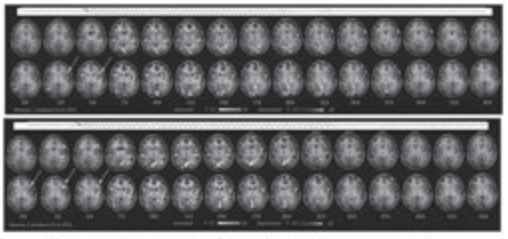

Sliding window analysis of 2 absences in the same patient

From: Moeller F et al. Epilepsia 2010

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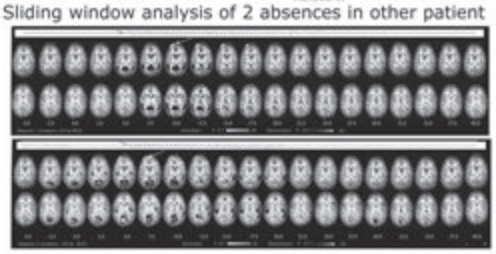
Sliding window analysis of 2 absences in other patient



Authors' conclusion: BOLD signal changes remarkably consistent in space and time in different absences of one patient but different from patient to patient despite similar EEG patterns and clinical semiology

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Moeller et al Absence seizures: individual patterns revealed by EEG-fMRI. *Epilepsia* 2010

- 17 absences from 9 patients studied
  - Identical findings in all absences of one individual
- Thalamic activation: 16 abs / 8 pts
- Default mode areas deactivation: 15 abs / 8 pts
- Caudate nucleus deactivation: 10 abs / 5 pts
- Cortical activation: 10 abs / 6 pts
  - Frontal: 5 pts
  - Parietal: 1 pt.
  - (no cortical activation: 3 pts)

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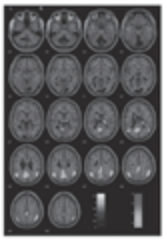
Benuzzi F et al, Epilepsia 2012; 53: 622-630: Changes of BOLD signal before and during absences: 15 Pat

<u>At onset of SW,</u> bilateral

- BOLD signal increase in
  - Thalamus
  - Cerebellum
  - anterior gyrus cinguli
- BOLD signal decrease in
  - medial prefrontal cortex
  - lateral parietal cortex
  - medial/posterior gyrus cinguli
  - Praecuneus
- (after preceding increase)



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Conclusion at present

- "Generalized" SW and absences are generated as resonance phenomena in a circuit comprising parts of the frontal, parietal and occipital cortex, default mode network (DMN) and anterior thalamus
- Triggered off from variable cortical loci (intraindividually consistent?)
- Precuneus the leading structure
- Pathological deactivation of the DMN explains absence?

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TV-induced seizures: photoparoxysmal EEG response

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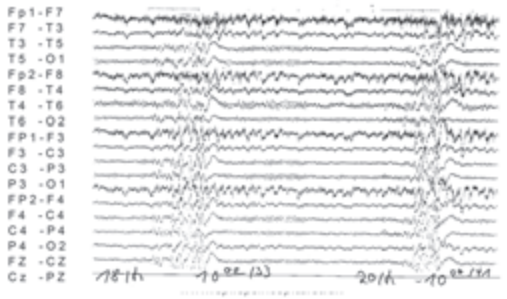

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Moeller et al (NeuroImage 2009) fMRI activation during spike and wave discharges evoked by photic stimulation

Comparison of BOLD signal 3 sec before photoparoxysmal response (PPR), i.e. at phase of synchronisation of cortical gamma oscillations preceding PPR (MEG)

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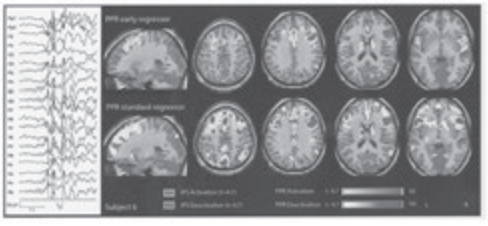
13 yr old boy, history of CAE, seizure free since 7 years, without drugs since 2 years. Spontaneous SW after sleep deprivation. Developed JME 6 mth later



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Authors' conclusion

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- "In contrast to spontaneous GSW, these results suggest that PPR (photoparoxysmal response) is a cortical phenomenon with an involvement of the parietal and frontal cortices."

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Thalamus, FS + absence: fMRI

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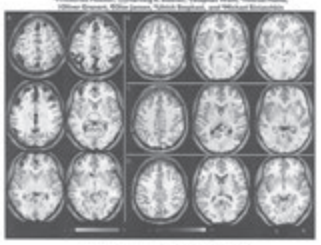
BRIEF COMMUNICATION

Mapping brain activity on the verge of a photically induced generalized tonic–clonic seizure



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Other reflex epileptic traits in IGE: - orofacial reflex myocloni (ORM)

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- Phenotypically identical with ORM in Primary Reading Epilepsy (PRE)
- 25 – 30% of JME patients
- Pathophysiology: interaction of complex functional anatomical network subserving formal processes of (written) language with short reflex loop = proprioception from speech musculature ⇒ myocloni in speech musculature
- No direct functional studies but probably largely identical with PRE

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ORM: ictal findings

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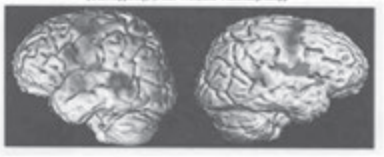
FULL-LENGTH ORIGINAL RESEARCH

Imaging seizure activity: A combined EEG/EMG-fMRI study in reading epilepsy



Reading-induced szs Language activations Motor mapping mouth/jaw

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"Reflex szs occur in RE when a critical mass of neurons are activated through a provoking stimulus within cortico-reticular and cortico-cortical circuitry subserving normal funtions." (Salek-Haddadi et al. Epilepsia 2009; 50:256-264)

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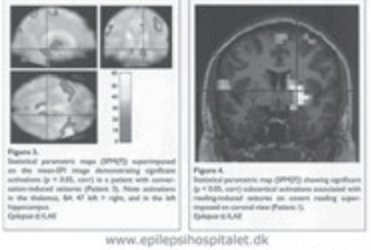

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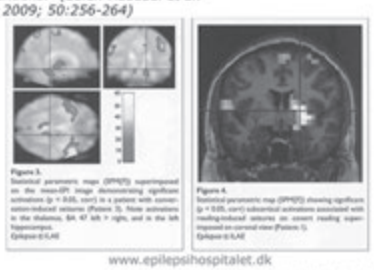

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Praxis induction

- Precipitation of seizures by cognition-guided complex motor tasks
- Most typical: complex visuo-motor coordination
- Matsuoka et al (2000): closely related to IGE. Found in 50% of JME patients in Japan
- 25 – 30% of JME patients in Germany (Mayer et al 2006) and Brasil (Sao Paolo group: Yacubian et al)
- Pathophysiology: interaction of complex functional anatomical network subserving visuomotor coordination with short reflex loop (proprioception ⇒ myocloni) in active musculature

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Seizure

Case report

Lego®-induced seizures
From an exceptional case towards the building blocks of generalised epilepsy

S.A. Zylka[a,*], H.M. Schippers[b,1], S.C. Tromp[c,2]

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Discussion

- "The traditional dichotomy between generalised and focal epilepsy can be questioned. There are specific (anatomical or physiological) areas within the brain functioning as one system. Patients with reflex seizures have sensitive areas within this system. Specific areas involved in sensory or cognitive tasks (the stimulus) overlap with the hyperexcitable area within this system and, therefore, the entire system can be influenced by the stimulus."

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Connectivity in JME


BRAIN

Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study

Christian Vollmar,[1,2,3] Jonathan O'Muircheartaigh,[4] Gareth J. Barker,[5] Mark R. Symms,[1,2] Pamela Thompson,[1,2] Veena Kumari,[6] John S. Duncan,[1,2] Dieter Janz,[7] Mark P. Richardson[3] and Matthias J. Koepp[1,2]

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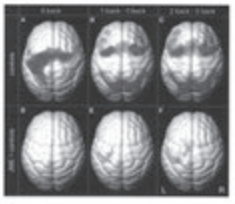
"Working memory paradigm": a spot appears in random sequence in one of 4 fields: where is it now? where was it last time? where the time before?

The more difficult the task, the more primary motor cortex and supplementary motor area become co-activated.
30 JME vs. 30 controls.
Motor response
Network working memory
JME minus controls



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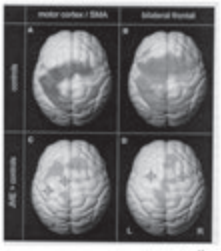
Vollmar et al. Motor system hyperconnectivity in JME: a cognitive fMRI study. Brain 2011; 134:1710-1719



Study: fMRI with an executive frontal lobe paradigm

Findings:

A+B: motor connectivity and working memory network in healthy controls

C+D: increased connectivity in JME patients

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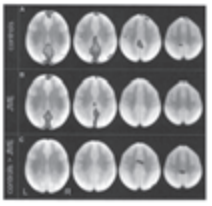
Concomitant deactivion of default mode network (frontopolar and præcuneus)

JME patients deactivate less

"An 'overload' of the task-positive cognitive network during a highly demanding task, together with impaired deactivation of the default mode network, could lead to hyperexcitability and hyper-connectivity across systems, including the motor cortex, and cause myoclonic jerks".



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Conclusion

- Here again, we see pathological activity in a functional anatomical system normally serving physiological function (complex visuo-motor coordination)
- = the probable basis for praxis induction

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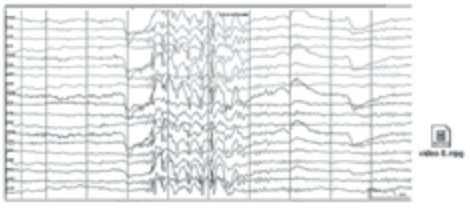
Eye closure sensitivity



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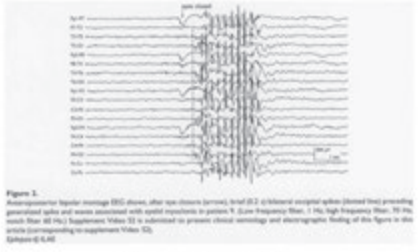
Viravan et al Jeavons syndrome existing as occipital cortex initiating generalized epilepsy. Epilepsia 2011; 52: 1273



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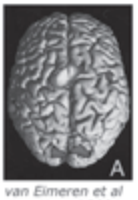
New study from S.Paolo (P.Oliveira da Conceição et al)

Findings:

- Myoclonias only with slow(voluntary or involuntary) eye closure(SMA), not with rapid blinks (physiological or nociceptive reflex (brain stem)
- Light required
- Myoclonias can occur without changes in scalp EEG
- Conclusion: eyelid reflex myocloni are generated not in OL but in SMA
- but visual system somehow involved



van Eimeren et al Ann Neurol 2001

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Reflex epileptic traits in IGE and their significance

- Photosensitivity (40-50%)
  - occipital ⇒ motor cortex
- Praxis induction (30-35%; Japan: 50%)
  - complex visuomotor coordination as "tuner" ⇒
  - sensorimotor reflex loop
- Orofacial reflex myoclonias (25-30%)
  - complex visuo-audio-motor "tuner" ⇒
  - sensorimotor reflex loop
- Eye closure sensitivity (20%)
  - sensorimotor reflex loop motor cortex, SMA!
  - some involvement of visual system

Conclusion: All reflex epileptic traits suggest interactions of functional anatomic networks or subsystems of the CNS

Ph.S indicator of upregulation occipito-frontal pathways?

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Conclusion on IGE: areas involved in corticothalamic and intracortical networks

- Thalamus (in particular nc. reticularis)
- Frontal cortex (frontopolar; ventromedial; supplementary motor area; primary motor cortex+?)
- Parietal cortex
- Precuneus
- Default mode areas
- Occipital cortex (photosensitive patients +?)
- Colliculi superiores (photosensitive patients)
- Lateral geniculate body (photosensitive patients)

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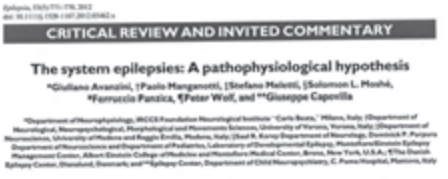

CRITICAL REVIEW AND INVITED COMMENTARY

The system epilepsies: A pathophysiological hypothesis

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The new view of IGEs: system epilepsies

- Epilepsies, usually idiopathic, where the ictogenic mechanisms use pre-existing functional anatomical networks that normally subserve physiological function.
- Well-demonstrated by reflex epileptic seizures
- *Avanzini G, Manganotti P, Meletti S. Moshé SL, Panzica F, Wolf P, Capovilla G. The system epilepsies: a patho-physiological hypothesis. EPILEPSIA 2012;53:771-778*

Examples of neurological system disorders?

Motoneuron disease – Polyneuropathies - Myasthenia gravis

System epilepsies

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Development of view of focal ictogenesis

- Traditional view: there is an epileptic focus, i.e. a small aggregate of abnormally functioning neurons that start to produce spikes which spread from there.
- Usually there is also a local lesion, the more likely to be found the better your tools of investigation.
- More recent view: in focal lesional epilepsies seizures originate in consequence of an interplay of ictogenic tissues in or adjacent to the lesion, with normal tissue more or less close by.
- There is excess of excitation in the shape of epileptic discharge, and there is inhibition (which also may be in excess) that contributes to the synchronisation which is a central feature of ictogenesis.

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Focal ictogenesis: investigation methods

- SPECT (interictal vs ictal) and PET
- Intracranial EEG recordings during preoperative monitoring
- EEG combined with MEG
- Connectivity study by graph analysis of ECoG
- fMRI
  - combined with EEG source analysis
  - sequential analysis
  - Diffusion tensor imaging / tractography
  - triggered by EEG

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Focal ictogenic networks

- The networks around focal epileptic lesions are quite widespread
- It is not yet quite clear to what extent they represent excitation and to what extent, inhibition
- Inhibition contributes to synchronisation and is, thus, an important factor of ictogenesis

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fMRI group analysis of 32 TLE pts. 3,5 a.7 sec after interictal discharge

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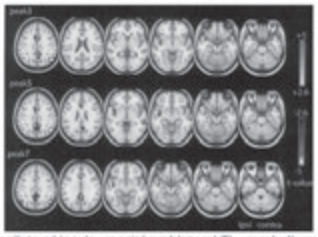

Activation: *ipsilateral* insula, mesial and lateral TL, cerebellum, *bilateral* mid-cingulate gyrus
Deactivation: *bilat.* inferior parietal lobules, posterior cingulate gyrus, precuneus, *contralat.* post. temp. cortex *Fahoum et al Epilepsia 2012*

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14 pts with frontal lobe epilepsy

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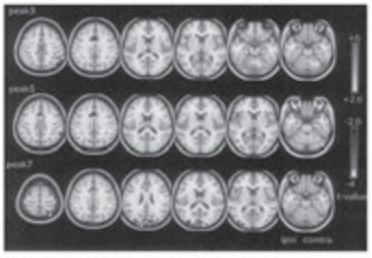

Activation: *bilateral* cingulate gyrus, *ipsilat* frontal operculum,medial thalamus, internal capsule, *contralat* cerebellum
Deactivation: *bilateral* cuneus, *contralat* inf and sup parietal lobules

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20 pts with posterior cortical epilepsies

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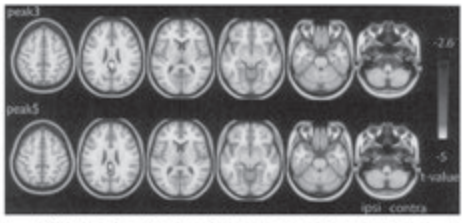

Bilateral deactivation clusters in posterior cingulate cortex and precuneus

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Interictal connectivity in focal epilepsies

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- Mesial temporal lobe epilepsy which is little prone to exogenous influences shows *decreased* connectivity with functionally related regions (prefrontal cortex, contralateral MTL, default mode network, brain stem): *Pittau et al, EPILEPSIA 2012; 53: 1013-1023 (EEG-fMRI study)*
- Opposed to *increased* functional connectivity in JME

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Pittau et al findings

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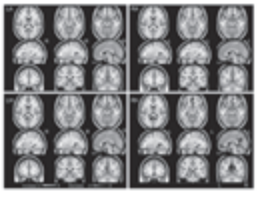
- For RA and RH, functional connectivity is significantly decreased in the brain areas of the DMN, the ventromesial limbic prefrontal regions, and the contralateral mesial temporal structures;
- For LA and LH, a significant decreased connectivity is present in DMN and contralateral hippocampus. Additional decreased connectivity is found between LA and pons and between LH and ventromesial limbic prefrontal structures.



Subtraction TLE pts fom healthy controls

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Voets et al (Montreal): study using diffusion tensor imaging

Structural substrates for resting network disruption in temporal lobe epilepsy

Natalie L. Voets,[1,2] Christian F. Beckmann,[3,4,5] David M. Cole,[3] Seokjun Hong,[1] Andrea Bernasconi[1] and Neda Bernasconi[1]

"Patients showed altered (typically reduced) functional connectivity between the hippocampus, anterior temporal, precentral cortices and the default mode and sensorimotor networks"

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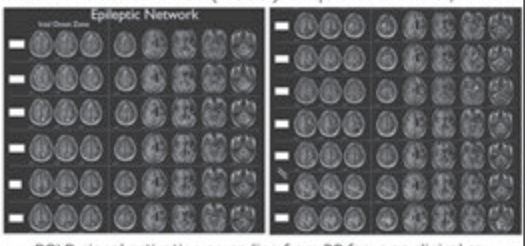
Ictal: Donaire et al (2009) sequential fMRI,rPLsz



BOLD signal activation spreading from RP focus as clinical sz spreads; concomitant contralateral BOLD signal decrease.

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Focal ictogenesis in idiopathic LREs

- There is no lesion or constant epileptic focus
- Seizures can be generated in alternate sides
- Very little investigated
- Ictal EEG in BECTS, topographic mapping (Jung et al 2003): Rolandic spikes originate from sulcal or gyral cortices on either side of the central sulcus, propagation from central to mid-temporal locations across the central sulcus by intracortical spreading

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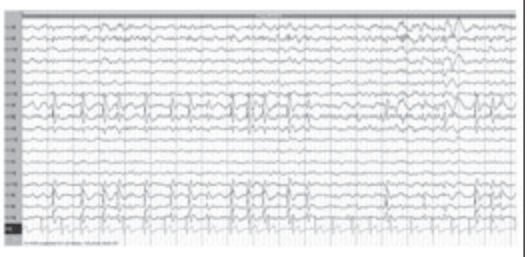
Rolandic seizure, ictal EEG



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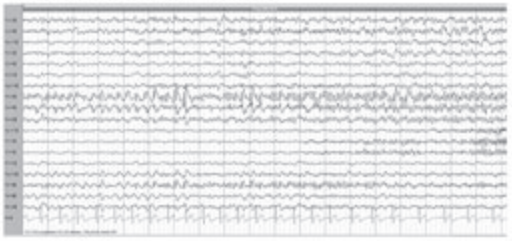
Rolandic seizure (cont)



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Ictogenesis in idiopathic LREs

Components

- Somatosensory system (contralateral spikes evoked by tapping or electrical stimulation, Manganotti et al 1998)
- Onset in sensory cortex ⇒ motor cortex? (Kellaway 2000)
- Close relation to sleep-regulating thalamic nuclei: high correlation of CT spikes with spindle avtivity (Nobili et al 1999)
- Age-dependence: functional instability of immature systems in the developing brain (Avanzini et al 2012)

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Conclusion

Ictogenesis of focal seizures in Rolandic epilepsy totally different from symptomatic focal epilepsies

Uses physiological functional anatomical networks

Idiopathic LREs are "system epilepsies" (Avanzini et al 2012)

Examples of neurological system disorders

Motoneuron disease

Polyneuropathies

Myasthenia gravis

System epilepsies

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Ictogenesis in focal and system epilepsies

Focal epilepsies

- Onset defined by focus
- Onset, often also evolution restricted to one hemisph.
- Pathogenic networks individual, fundamentally de novo, although pre-existent circuits may be recruited

System epilepsies

- Possible trigger zones variable within network
- Involvement of distributed bilateral (symmetric or asymmetric) selective cortical-subcortical networks
- Using pre-existent , syndrome-specific physiological systems

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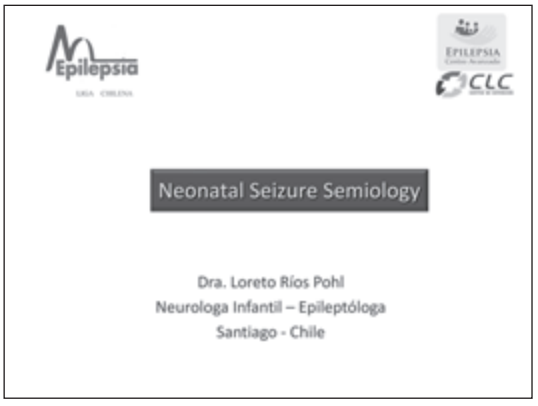
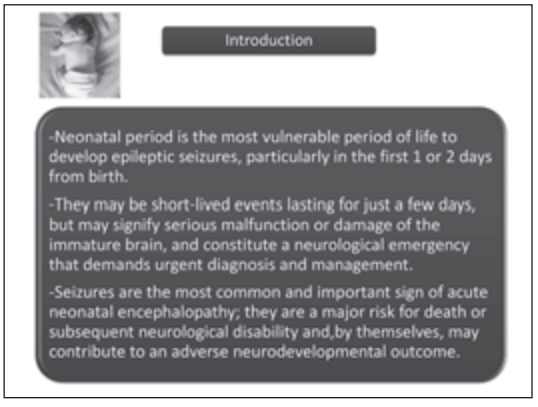
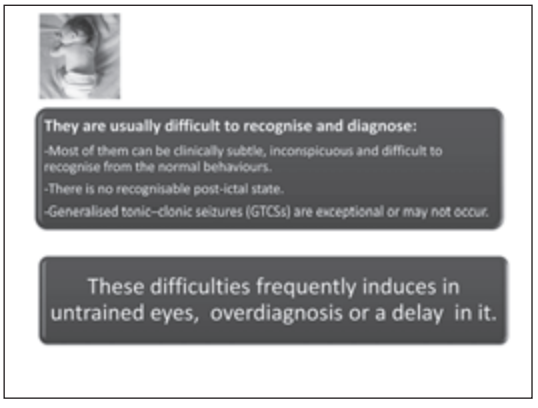
Loreto Rios (Chile)

NEONATAL SEIZURES







Neonatal Seizures (NN Sz)

Definition: paroxysmal, repetitive and Steriotyped events, secondary to an excessive discharge of cortical neurons

Occur during the neonatal period

-Term neonates (TNN) from birth until 28 days.
-In preterm neonates (PTNN), should be considered conceptional age.

NN Sz. are surrogate markers for prenatal and/or neonatal brain disorders, and predict later neurological sequelae

Duration of neonatal seizures

They are usually brief (10 s to 1-2 min)

Longer seizures and status epilepticus develop more readily at this age, but...

... is not as severe as in older ages.

Epidemiology

Prevalence 1,5%

Incidence: 1,8 a 3,5/1000 RNV

In PTNN incidence increases to 57-132 per 1000 births.

Etiology

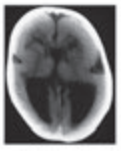
Hypoxic-ischemic encephalopathy (50- 80%)

Intracranial hemorrhage and Stroke (15%)

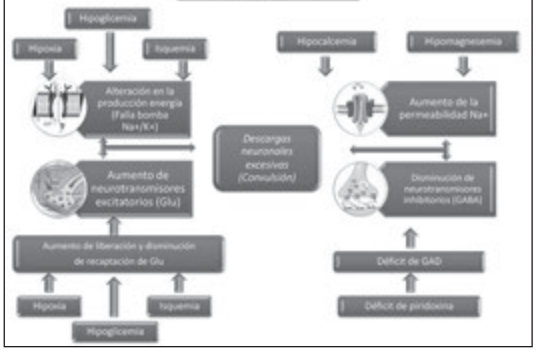
Metabolic:
- hypoglycemia
- hypocalcemia
- HipoMg, HipoNa
- Hiperamonemias organic aciduria
- Pyridoxine deficiency

Etiology Neonatal Seizures

- Infections (5 a 10%)
- brain malformations
- Drug Deprivation
- neurocutaneous syndromes
- Inadvertent administration of local anesthetics during childbirth
- Neonatal epilepsy Syndromes



Pathophysiology



Semiology

Neonatal Seizure Clasification

Volpe Scheme *

- -Subtle seizures (50%)
- -Tonic seizures (5%)
- -Clonic seizures (25%)
- -Myoclonic seizures (20%)
- -Non-paroxysmal repetitive behaviours.

Mizrahi Scheme

- motor automatisms (which include ocular signs, and oral–buccal–lingual, progression and complex purposeless movements).
- -Focal tonic
- -Generalised tonic
- -Focal clonic
- -Myoclonic
- -spasms

Neonatal Sz

Main Seizures			
Sublte 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

Neonatal Sz

Main Seizures			
Sublte 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

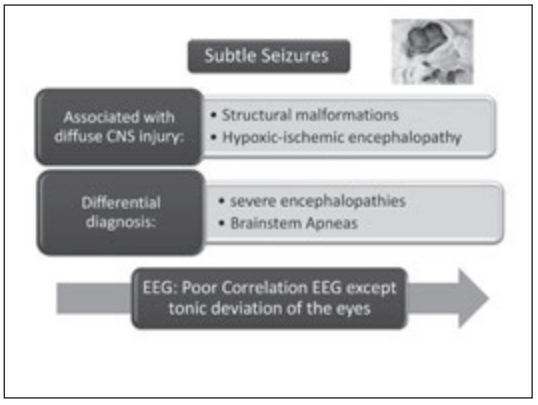
Subtle Seizures

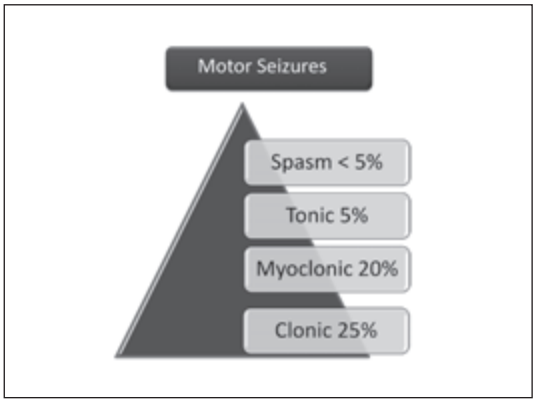
- Episodes minimum, fragmentary, and stereotyped periodic paroxysms of normal movements.
- Most frecquent type of seizure (specially in TNN)
- Corresponding to 50% of Neonatal Sz.
- They imitate normal behaviours and reactions.

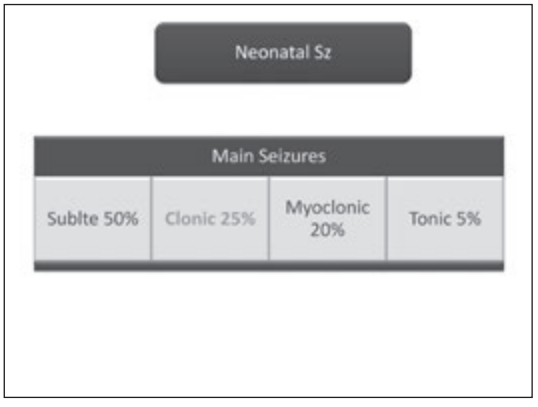
Subtle Seizures

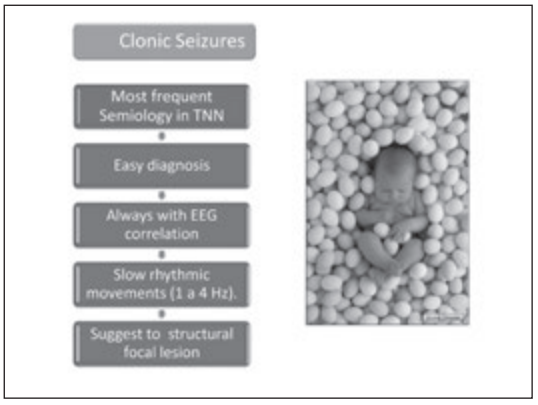
Clinical Manifestations:

- Ocular movements:
  - Random and roving eye movements to sustained conjugate tonic deviation with or without jerking.
  - Eyelid blinking or fluttering.
  - eyes rolling up, eye opening, fixation of a gaze or nystagmus may occur alone or with other ictal manifestations
- Oral–buccal–lingual movements (sucking, chewing,smacking and tongue protrusions)
- Progression movements (rowing, swimming, pedalling, bicycling, thrashing or struggling movements)
- Complex purposeless movements (sudden arousal with episodic limb hyperactivity and crying)


Subtle Seizures
Associated with diffuse CNS injury:
• Structural malformations
• Hypoxic-ischemic encephalopathy
Differential diagnosis:
• severe encephalopathies
• Brainstem Apneas
EEG: Poor Correlation EEG except tonic deviation of the eyes


Motor Seizures
Spasm < 5%
Tonic 5%
Myoclonic 20%
Clonic 25%


Neonatal Sz
Main Seizures
Sublte 50%
Clonic 25%
Myoclonic 20%
Tonic 5%


Clonic Seizures
Most frequent Semiology in TNN
Easy diagnosis
Always with EEG correlation
Slow rhythmic movements (1 a 4 Hz).
Suggest to structural focal lesion

Clonic Seizures can be:

- Multifocal (Several segments, not Jacksonian migratory pattern)
- Focal (Face, Neck, Trunk or body extrimities)

Clonic Seizure Etiology

Severe CNS involvement :	Metabolic Alterations:
-Structural (malformations, cortical dysplasias)	-Transient (hypoglycemia, hypocalcemia)
-Hypoxic-ischemic (EHI)	-Persistent (EIM)

Diferential Diagnosis:

- Neonatal tremor

Neonatal Sz

Main Seizures			
Sublte 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

Myoclonic Seizures

Semiology

- Sudden movements in flexor muscles of the extremities
- Uncommon in the NN
- Usually during sleep.

3 tipos

- Focal: flexor muscles of an upper limb
- Multifocal: abrupt asynchronous contractions of different parts of the body.
- Generalised: bilateral myoclonus of upper limbs and somentimes lower limbs also.

Myoclonic Seizures

Etiology:
Always must think in EIM

EEG:
- Burst- Suppression

Diferential Dignosis:
- Neonatal benign myoclonus
- Benign myoclonus during sleep.

Neonatal Sz

Main Seizures			
Sublte 50%	Clonic 25%	Myoclonic 20%	Tonic 5%

Tonic Seizures:

- Sustained posture of trunk and / or extremities, associated or not with tonic oculo-cefalic deviation.

Tonic Seizures

- **Focal:**
  - Slow and maintained asymmetric changes of posture
  - cyanosis and apnea is frequent associated
  - Good Clinical EEG correlation
- **Generalized:**
  - Most frequent presentation
  - Tonic extention of upper an lower extremeties
  - EEG pattern: Burst Suppresion

Tonic Seizures

- **Etiology:**
  - Severe CNS involvement
- **Differential diagnosis:**
  - Decerebrate postures / decortication
  - Stiff-baby syndrome

Autonomic ictal manifestations

Commonly occur with motor manifestation in 37% subtle Sz → Paroxysmal changes of heart rate, respiration and systemic blood pressure → Apnea* Salivation Pupillary changes Are common

Duration of neonatal seizures

NN Sz are usually brief (10 s to 1-2 min) → Longer seizures and status epilepticus develop more readily at this age → Convulsive NN status epilepticus is not as severe as in older ages.

Non-epileptic neonatal seizures

- They looks like subtle , tonic or Myoclonic Sz. but are not associated with ictal EEG discharges
- Exaggerated reflex behaviours 'brain-stem release phenomena'
- Correlate with diffuse abnormal brain processes (HIE) and a poor short-term outcome.
- EEG Pattern
  Suggestive of forebrain deppresion

Neonates Epileptic Syndromes

Síndromes epilépticos del RN

Convulsiones neonatales benignas:	• No familiares • Familiares
Encefalopatias epilépticas:	• Encefalopatía mioclónica temprana • Síndrome de Ohtahara

Síndromes epilépticos del RN

Convulsiones neonatales benignas:	• No familiares • Familiares
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Benign non familial neonatal seizures (BnFNS)

"Fifth day Seizures"
• Between the day 3 and 7 (30% between 4 y 6)

male: female = 2 : 1

7% Neonatal Sz.

Benign non familial neonatal seizures (BnFNS)

Seizures:

- Face and limbs unilateral Clonic Sz. (rare bylateral)
- Apnea (30%)
- Bursts of 1-3 minutes , developing a clonic status of 2 hours to 3 days.

Etiology:

- Unclear: Its been associated to Zn deficiency and rotavirus infection.

Benign non familial neonatal seizures(BnFNS)

EEG:
• Slow activity and interictal spikes during waking and sleep.

Prognosis:
• Normal or near normal development. No reoccurrence of Sz.

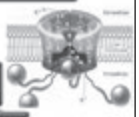
Treatment:
BZD en prolonged seizures

The diagnosis key is the starting time and tonic Sz. Absence.

Síndromes epilépticos del RN

Convulsiones neonatales benignas:	• No familiares • Familiares
Encefalopatías epilépticas:	• Encefalopatía mioclónica temprana • Síndrome de Ohtahara

Familiar Neonatal Seizures (BFNS)



- infrequent
- Autosomal dominant: KCNQ2 (20q) - KCNQ3 (8q)
- Brief Sz, frequent since the first week of life (30% before 2 months)
- Normal NN, without risk factors.
- male= female

Familiar Neonatal Seizures (BFNS)

Seizures:
- Tonic
- Apnea followed with vocalisations.
- Ocular movements.
- Motor and oroingual automatism
- Asymmetric Clonic Sz

→ **Laboratory and imagen study:**
- normal

→ **EEG: Mainly normal.**

Familiar Neonatal Seizures (BFNS)

Treatment: FAE do not change the course of the disease or modify the prognosis

The key for the diagnosis is the similar family history, however the diagnosis must be of exclusion.

Pronosis:
- Generally cease 1 to 6 months after started.
- 10-14% will develop seizures later on.

Benign Neonatal seizures : Non familar vs Familiar

	BnFNS	BFNS
Sz type	Clonic	Tonic- clonic
Starts	5th day	2d a 3th day
Duration	Status (X=20 hrs)	Brief, frequent
Etiology	Unknown	autosomal dominant
Epilepsy	0,5%	11%
Ictal EEG	Focal Spikes	voltage depression
Psychomotor delay	Mild	No deficit

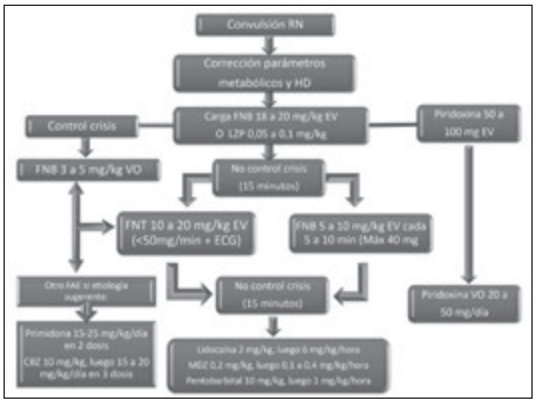
Síndromes epilépticos del RN

Benign neonatal convulsions:	• Familiar • Non familiar
Epileptic encephalopathies:	• Encefalopatía mioclónica temprana • Ohtahara Syndrome

Prognosis

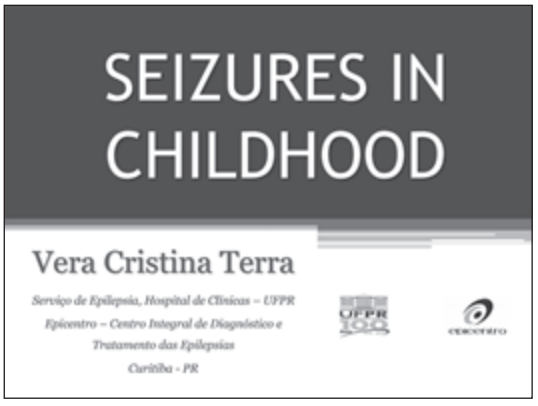
Treatment

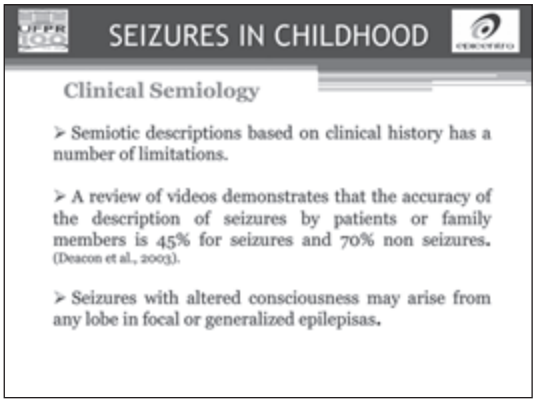
Early detection and management of underlying cause:	• Correction metabolic and hemodynamic parameters • Treatment of infection if any
Use of AED´s:	• Intravenous(No IM) • Relatively higher doses than usual

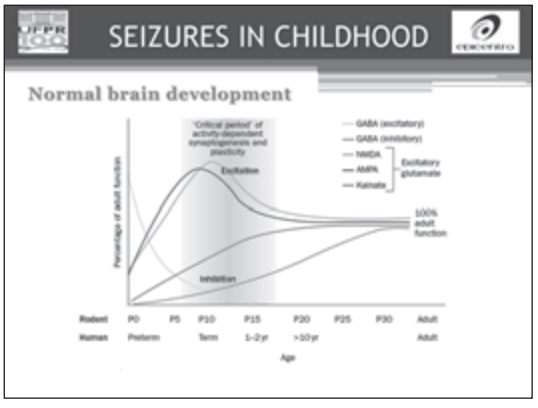


Vera Terra (Brazil)

SEIZURES IN CHILDHOOD







SEIZURES IN CHILDHOOD

Epilepsy and epileptogenesis

Development of synaptic processes.
myelination
Dendritic branching.
Morphology of dendritic spines
Development of synapses
neurotransmitters

Changes in seizure semiology with age

Vera Cristina Terra

SEIZURES IN CHILDHOOD

Epilepsy and epileptogenesis

The same etiology can cause various clinical symptoms?

Intrinsic epileptogenicity of lesions

Ex: MTS, MCD

SEIZURES IN CHILDHOOD

TABLE 1. Value of Positive and Negative Motor Signs in Lateralizing Seizure Onset to the Right or the Left Hemisphere

Sign	Hemisphere of Seizure Onset	Observed Rate	Positive Predictive Value*
Positive motor signs			
Early nonforced head turn	Ipsilateral	30%	
Late contraversive forced head turn	Contralateral	25%–50%	
Late ipsiversive forced head turn	Ipsilateral		
Eye deviation	Contralateral	Rarely solitary	High if occipital
Focal clonic	Contralateral	30%	>95%
Asymmetric clonic ending	Ipsilateral	70% of secondary generalized seizures	83%
Dystonic limb	Contralateral	67%	93%
Tonic limb	Contralateral	13%	85%
Complex postures			
M2E and fencing	Contralateral	3% of temporal, 25% of frontal patients	90%
"Figure 4" sign	Contralateral to extended limb	70% of seizures generalizing from temporal lobe, 31% of extratemporal	89%
Negative motor signs			
Ictal paresis or immobile limb	Contralateral	3% of complex partial seizure patients	100%
Todd paresis	Contralateral	13% of partial seizure patients	80%–100%

*The positive predictive value is the number of true positives divided by the sum of true positives and false positives.

(So, 2006)

SEIZURES IN CHILDHOOD

TABLE 2. Importance of Automatisms, Autonomic Signs, and Peri-ictal Speech Signs in Hemispheric Lateralization or Lobar Localization of Partial Seizures

Characteristic	Location*
Automatisms	
Unilateral limb automatisms	Ipsilateral to seizure focus, 90% PPV
Unilateral eye blinks	Ipsilateral to focus, 83% PPV
Postictal cough	40% of temporal lobe seizure patients, 3% of pseudoseizure or frontal lobe seizure patients
Postictal nose wiping	50% of temporal and 10% of frontal lobe seizures; 90% PPV
Bipedal automatisms	30% of frontal and 10% of temporal lobe seizure patients
Ictal spitting or drinking	Rare, but high association with right temporal seizures
Automatisms with preserved responsiveness	Nondominant (usually right) temporal or extratemporal on either side
Gelastic seizures	Hypothalamic, sometimes mesial temporal or frontal cingulate origin
Autonomic signs	
Ictus emeticus	Rare, but usually right temporal
Ictal urinary urge	Rare (2%), but localizes to right temporal
Piloerection (goose bumps)	Mostly left temporal
Peri-ictal speech	
Ictal speech arrest	Seen in 73% of temporal lobe seizure patients, but only 67% PPV for dominant hemisphere focus
Ictal speech preservation	Seen in only 13%, but PPV of 83% for non-dominant hemisphere focus in temporal lobe seizure patients
Postictal dysphasia	90% dominant hemisphere involvement

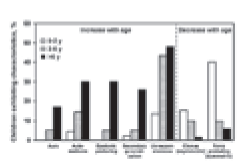


FIGURE 2. Seizure characteristics that change with age. (Modified from Nordli et al., 2001. Used with permission.)

(So, 2006)

SEIZURES IN CHILDHOOD

In Children...

Semiology	Generalized	Frontal	Temporal	Parietal	Occipital	Multilobar	Total
Aura	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Clonic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tonic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tonic-clonic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Automatism	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hypermotor	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gelastic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Dyscognitive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Atonic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Hypomotor	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Myoclonic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Versive	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Epileptic spasms	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* $p < 0.05$ (Binomial test).
** $p < 0.01$ (Binomial test).
*** $p < 0.001$ (Binomial test).

SEIZURES IN CHILDHOOD

Natural hystory of epilepsy

- Recurrence of a single seizure in 2 years :

32%: idiophatic epilepsies.

57%: symptomatic epilepsies. (Berg & Shinnar, 1991)

- Risk factors after the onset of epilepsy*Número de* Seizures in the first 6 months.

Response first AED.

SEIZURES IN CHILDHOOD

Semiology

- **Neonatal period:** Cardiovascular changes, cycling, hypomotor crises.
- **Until 6 mo:** Rare focal seizures, epileptic spasms still occur, awakenings.
- **2 years:** symmetric tonic seizures as a manifestation of focal seizures. Action of subcortical structures and the brain stem?
- Seizures with less exuberant motor components.

SEIZURES IN CHILDHOOD

Semiology

3-6 years

- Phenomena tonic, clonic, myoclonic, atonic.
- Epileptic spasms.
- Hypermotor seizures.
- Oroalimentar and simple gestural automatisms.
- Forced unilateral blink.

SEIZURES IN CHILDHOOD

Semiology

After 7 years

- More complex automations.
- Less frequent phenomena tonics.
- Dystonic posturing.
- Increased incidence of generalized tonic-clonic seizures.

SEIZURE

LOBAR LOCALIZING SIGNS IN ICTAL SEMIOLOGY

Ictal semiology; lobar localization

Temporal lobe localization
- Aura characteristics
  - Epigastric rising; olfactory, dysgeusic, auditory hallucinations
  - "Experiential—déjà[jamais-vu; dissociative symptoms
- Oral and/or manual automatisms
- Dystonic hand posturing
- Ictal spitting, postictal nose wiping
- Postictal confusion lasting several minutes
- Postictal aphasia present (if dominant hemisphere involved)

Frontal lobe localization
- Explosive onset
- Hypermotor activity
- Lower extremity automatisms (bicycling, kicking)
- Nocturnal seizure clustering of several per night
- Brief or absent postictal confusion
- Postictal aphasia infrequent unless primary language cortex involved

Occipital lobe localization
- Unilateral simple visual hallucinations (shapes and colors)
- Eye deviation
- Nausea/vomiting, migraine in children

Peri-Rolandic localization
- Unilateral clonic activity as earliest seizure manifestation
- Unilateral sensory disturbance as earliest seizure manifestation
- Todd's paralysis

SEIZURES IN CHILDHOOD

Table 3. Electroclinical syndromes and other epilepsies

Electroclinical syndromes arranged by age at onset[a]
- Neonatal period
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders

SEIZURES IN CHILDHOOD

Table 3. Electroclinical syndromes and other epilepsies

- Childhood
  - Febrile seizures plus (FS+) (can start in infancy)
  - Panayiotopoulos syndrome
  - Epilepsy with myoclonic atonic (previously astatic) seizures
  - Benign epilepsy with centrotemporal spikes (BECTS)
  - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
  - Late onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
  - Landau-Kleffner syndrome (LKS)
  - Childhood absence epilepsy (CAE)

SEIZURES IN CHILDHOOD

Table 3. Electroclinical syndromes and other epilepsies

- Adolescence – Adult
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic–clonic seizures alone
  - Progressive myoclonus epilepsies (PME)
  - Autosomal dominant epilepsy with auditory features (ADEAF)
  - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies

SEIZURES IN CHILDHOOD

Table 3. Electroclinical syndromes and other epilepsies

- Distinctive constellations
  - Mesial temporal lobe epi… sclerosis (MTLE with HS)
  - Rasmussen syndrome
  - Gelastic seizures with hypoth…
  - Hemiconvulsion–hemiplegia–…
  - Epilepsies that do *not* fit into a… distinguished first on the bas… structural or metabolic cond… basis of the primary mode of seizure onset (generalized vs. focal)

Constellation: Apparent clustering of clinical signs and symptoms, but without the genetic characteristics of the syndromes. Are distinct enough to be considered as specific clinical entities

SEIZURES IN CHILDHOOD

Table 3. Electroclinical syndromes and other epilepsies

- Epilepsies attributed to and organized by structural-metabolic causes
  - Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
  - Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
  - Tumor
  - Infection
  - Trauma
- Angioma
  - Perinatal insults
  - Stroke
  - Etc.

SEIZURES IN CHILDHOOD

Table 3. Electroclinical syndromes and other epilepsies

- Epilepsies of unknown cause
- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
  - Benign neonatal seizures (BNS)
  - Febrile seizures (FS)

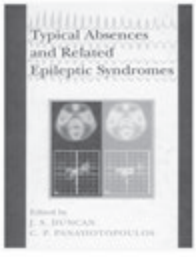
SEIZURES IN CHILDHOOD

Childhood absence epilepsy

- 2-8 years, 6-7 years peak.
- Very frequent absence seizures may be present.
- Female.
- Genetic predisposition.
- EEG: CPO regular 3 Hz.
- TC seizures in adolescence.

SEIZURES IN CHILDHOOD

Panayiotopoulos et al., 1989



- All absence epilepsies are similar?

SEIZURES IN CHILDHOOD

Absence epilepsy with eyelid myoclonia

SEIZURES IN CHILDHOOD

Myoclonic absence

Tassinari et al., 1969.

- 2-9 years.
- Absences with massive myoclonia in cephalic segment and upper limbs and tonic contraction.
- Refractory to antiepileptic drugs.
- EEG: spike and wave at 3 Hz.

SEIZURES IN CHILDHOOD

Atypical Absence

SEIZURES IN CHILDHOOD

Focal Idiopathic Epilepsies

- BCE – rolandic form.
- Occipital early onset epilepsy – Panayiotopoulos.
- Occipital late onset epilepsy – Gastaut.
- Atypical benign epilepsy.

SEIZURES IN CHILDHOOD

Benign Childhood Epilepsy

- Affect 22% of children with non-febrile seizures.
- Children clinically normal / normal picture.
- Favorable outcome: consider seizure frequency and cognitive aspects.

SEIZURES IN CHILDHOOD

Benign Childhood Epilepsy

- Prognosis – BCE with centro-temporal spikes:
  - 10-20% with frequente seizures.
  - 1% evolve to more severe forms of epilepsy.

SEIZURES IN CHILDHOOD

Benign Childhood Epilepsy

- Prognosis – Panayiotopoulos Syndrome
  - 25% with frequente seizures.
  - 10% with seizures lasting longer period of time.
  - Atypical evolution in < 3%.

SEIZURES IN CHILDHOOD

EPILEPSIA BENIGNA DA INFÂNCIA

- Prognosis – BCE with occipital spikes (Gastaut):
  - 40 - 50% with rare CPS or TC seizures CPS e CTCG.
  - Atypical evolution is rare.

SEIZURES IN CHILDHOOD

SHORT COMMUNICATION

Oxcarbazepine and atypical evolution of benign idiopathic focal epilepsy of childhood

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Patients that have benign epilepsy with centrotemporal spikes (BECTS) may occasionally experience an atypical development in their course when treated with drugs such as carbamazepine.

with centrotemporal spikes, drug-induced seizures, oxcarbazepine

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Accepted 7 October 2005

manifested atypical absences, neuropsychological disturbances, and generalized spike-and-wave discharges in their electroencephalograms (EEGs) that became continuous during sleep. The third patient showed, during OXC therapy, more frequent partial motor seizures which ended with ictal vomiting and post-ictal obnubilation. EEGs recorded during sleep showed discontinuous paroxysmal activity in the right centro-temporal area. Symptoms were reversed following discontinuation of the OXC therapy. Although electroclinical findings were consistent with a BECTS diagnosis, all patients had some atypical features. Our observations show that BECTS patients, in particular those presenting with atypical findings, might be at risk for developing paradoxical reactions to OXC therapy. We suggest that OXC should be included in the list of drugs that may cause electroclinical deterioration in these patients.

SEIZURES IN CHILDHOOD

Table 4. Comparison of recommendations for the treatment of pediatric epilepsy.

Seizure type or epilepsy syndrome	U.S. pediatric expert consensus survey	European pediatric expert consensus survey	ILAE	SIGN	NICE	French study	FDA approved
Partial-onset	OXC, CBZ	OXC, CBZ	A: OXC; B: none C: CBZ, PB, PHT TPM, VPA	PHT, VPA, CBZ, LTG, TPM, OXC, VGB, CLB	CBZ/VPA, LTG, OXC, TPM	OXC, CBZ, LTG (adult males)	PB, PHT, CBZ, OXC, TPM
BECT	OXC, CBZ	VPA	A, B: none C: CBZ, VPA	Not specifically mentioned	CBZ, OXC, LTG, VPA	Not surveyed	None
Childhood absence epilepsy	ESM	VPA	A, B: none C: ESM, LTG, VPA	VPA, ESM, LTG	VPA, ESM, LTG	VPA, LTG	ESM, VPA
Juvenile myoclonic epilepsy (JME)	VPA, LTG	VPA	A, B, C none	VPA, LTG, TPM	VPA, LTG	VPA, LTG	TPM, LTG, LEV
Lennox-Gastaut syndrome	VPA, TPM	VPA	Not reviewed	Not specifically mentioned	LTG, VPA, TPM	Not surveyed	FLB, TPM, LTG
Infantile spasms	VGB, ACTH	VGB	Not reviewed	Not specifically mentioned	VGB, corticosteroids	Not surveyed	None

Wheless et al, 2007

SEIZURES IN CHILDHOOD

Focal epilepsies undoubtedly or probably symptomatic

Limbic epilepsy:

- Medial Temporal lobe epilepsy with hippocampal sclerosis.
- Medial Temporal lobe epilepsy defined by specific etiologies.

SEIZURES IN CHILDHOOD

Focal epilepsies undoubtedly or probably symptomatic

Neocortical epilepsy

Frontal lobe

Temporal lobe

Parietal lobe

The occipital lobe

Focal epilepsies with specific forms of precipitation

SEIZURES IN CHILDHOOD

Frontal Lobe Epilepsies

- Supplementary motor area.
- Cingulate.
- Fronto-polar.
- Orbitofrontal.
- Dorsolateral.
- Opercular.
- Motor cortex.

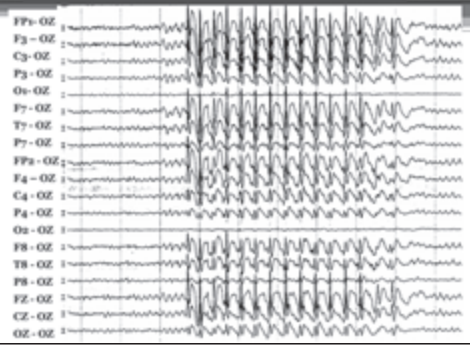
SEIZURES IN CHILDHOOD

IDIOPATHIC EPILEPSIES (GENETIC)

SEIZURES IN CHILDHOOD

Childhood Absence

SEIZURES IN CHILDHOOD



SEIZURES IN CHILDHOOD

Epilepsy Idiopathic Generalized

SEIZURES IN CHILDHOOD

SYMPTOMATIC EPILEPSIES

(STRUCTURAL / METABOLIC)

SEIZURES IN CHILDHOOD

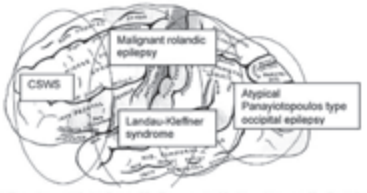


Figure 1 Epileptic encephalopathies or malignant epilepsies with electrical status epilepticus during sleep. Pathophysiology is quite the same, but symptoms are defined by the driver focus: prefrontal and frontal area in continuous spike-waves syndrome (CSWS), central region in malignant rolandic epilepsy, temporo-parietal location in Landau–Kleffner syndrome or more posterior in atypical Panayiotopoulos type occipital epilepsy.

K. van Rijckevorsel, Seizure (2006) 15, 227–234

SEIZURES IN CHILDHOOD

Myoclonic Astatic Epilepsy

SEIZURES IN CHILDHOOD

Lennox-Gastaut Syndrome

- from 1 to 8 years.
- Family history in 3-27% of cases.
- Generalized seizures and focal.
- Idiopathic x Symptomatic.
- Mental retardation.
- History of West syndrome: 30 to 40%.
- Treatment.

SEIZURES IN CHILDHOOD

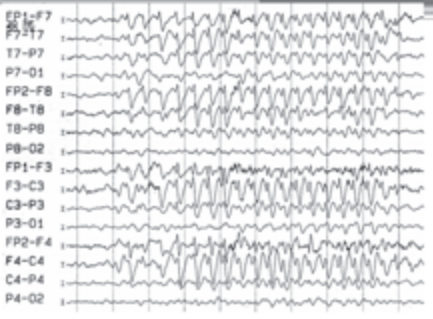
Lennox-Gastaut Syndrome

- Prognosis
- Rare total seizure control.
- Dependence on family care.
- Daily seizures.
- Earlier onset related to more severe mental retardation.
- Status epilepticus badly aggravates the evolution.

SEIZURES IN CHILDHOOD

Lennox-Gastaut Syndrome

SEIZURES IN CHILDHOOD



SEIZURES IN CHILDHOOD

Doose Syndrome (Myoclonic Astatic Epilepsy)

Drop	Astatic	Tonic
Duration of drop	Straight, directed to the buttocks. Depend on the center of gravity	Propulsive
Post-ictal confusion	Absente	Depends on seizure length, confusion and automatism may occur
Manifestation in supine position	Up ocular version	Trunk flexion and abduction of the upper limbs
Ictal EEG	Spike-wave complex; atenuation of background activity	Recrutant rhythm
Related syndrome	MAE	LGS

SEIZURES IN CHILDHOOD

FRONTAL LOBE EPILEPSY

SEIZURES IN CHILDHOOD

TEMPORAL LOBE EPILEPSY

SEIZURES IN CHILDHOOD

PARIETAL LOBE EPILEPSY

SEIZURES IN CHILDHOOD

OCCIPITAL LOBE EPILEPSY

SEIZURES IN CHILDHOOD

CONTINUOUS PARTIAL EPILEPSY

SEIZURES IN CHILDHOOD

HYPOTHALAMIC HAMARTOMA

SEIZURES IN CHILDHOOD

BRAINSTEM SEIZURES

SEIZURES IN CHILDHOOD

TUBEROUS SCLEROSIS

Diagnostic criteria for Tuberous Sclerosis according to the consensus conference of 1998 (two major criteria or one major and two minors).

Major criteria	Minor criteria
Facial angiofibroma or fibrous plaques	Multiple spots on the dentin
Non-traumatic periungual or ungueal fibromas	Hamartomatous rectal polyps
Shagreen plaques (connective tissue nevus).	Bone cysts
Multiple retinal nodular hamartomas.	Radial migration lines in central nervous system white matter (three or more lesions)
Cortical tubers	Gingival fibromas
Subependymal nodules	No rectal hamartomas
Subependymal giant cell astrocytoma	Achromatic retinal plaques
Single or multiple cardiac rhabdomyoma	Skin lesions confetti
Lymphangiomatosis	Multiple renal cysts
Renal angiomyolipoma	

CD and altered neuronal migration occurring associates are considered as only one criterion.

SEIZURES IN CHILDHOOD

NATURAL HYSTORY OF EPILEPSY

- **Mortality:**

Higher risk in the first 5 years of diagnosis and after 10 years of diagnosis.

Number of seizures in the first 6 months.

Response to AEDs.

SEIZURES IN CHILDHOOD

NATURAL HYSTORY OF EPILEPSY

- **Mortality – causes:**

Not related: tumors outside CNS, cardiac ischemia, pneumonia, etc..

Related to background disease: *cerebral tumors, cérebro-vascular diseases,* encephalitis, brain abscesses, metabolic diseases.

SEIZURES IN CHILDHOOD

NATURAL HYSTORY OF EPILEPSY

- **Mortality – causes:**

Related to epilepsy: suicide, adverse effects of AEDs, AED idiossincratic reactions, related seizures *per se*, (trauma, burns, drowning), status epilepticus, asphyxia, aspiration pneumonia after a seizure, *SUDEP*.

SEIZURES IN CHILDHOOD

Epilepsy is more than seizures. An ongoing epileptogenic process can irreversibly damage the brain, especially maturing brain, even if seizures are controlled or missing, and causes persistent cognitive changes and finally global intellectual deficits.

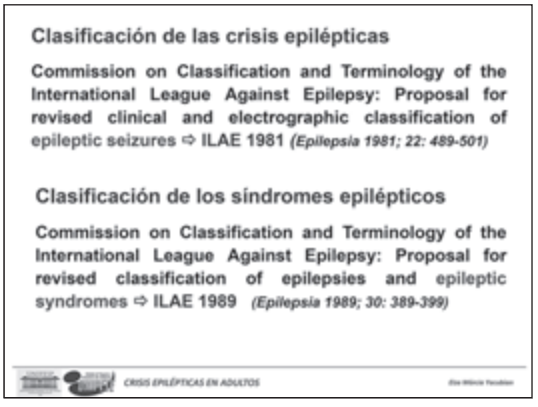
K. van Rijckevorsel; Seizure (2006) 15, 227–234

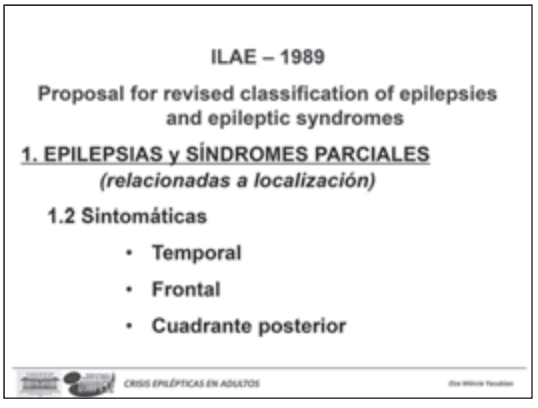
SEIZURES IN CHILDHOOD

THANK YOU

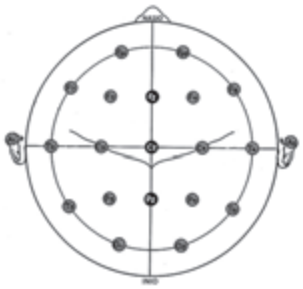
Elza Marcia Yacubian (Brazil)

SEIZURES IN ADULTS





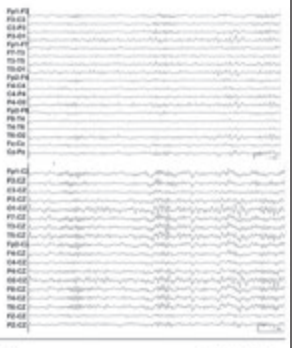
Sistema Internacional 10-20 para la colocación de los electrodos



- 21 electrodos
- Letras - regiones cerebrales subyacentes a los electrodos
  - ✓ frontopolar (Fp)
  - ✓ frontal (F)
  - ✓ central (C)
  - ✓ parietal (P)
  - ✓ occipital (O)
  - ✓ temporal (T)

JASPER, 1958; KLEM et al.1999

Montajes



ILAE – 1989

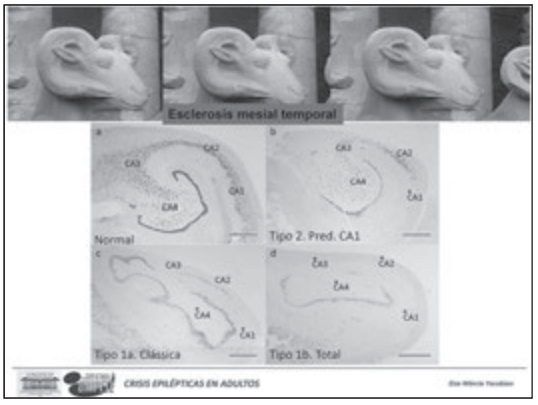
Proposal for revised classification of epilepsies and epileptic syndromes

1. EPILEPSIAS Y SÍNDROMES PARCIALES
(relacionadas a localización)

1.2 Sintomáticas

Temporal: mesial y lateral

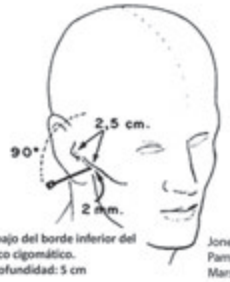
- ✓ Epilepsia del lóbulo temporal: epilepsia más común en adultos
- ✓ Esclerosis mesial temporal: sustrato patológico más frecuente



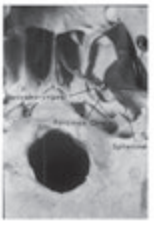
Epilepsia mesial del lóbulo temporal:

- EEG interictal:
  - ondas agudas en la región temporal anterior
  - ondas lentas temporales
- EEG ictal: ritmo teta ictal
- RM: esclerosis hipocampal

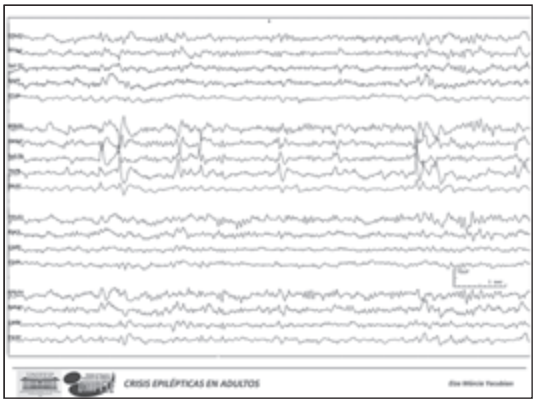
ELECTRODOS BASALES ESFENOIDALES

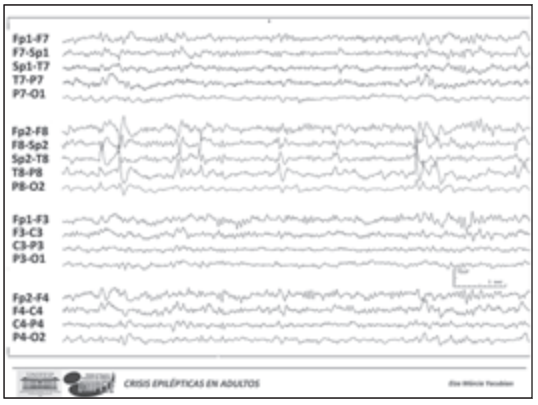


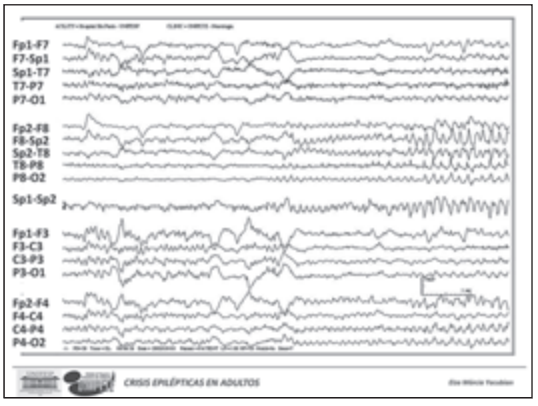
Abajo del borde inferior del arco cigomático.
Profundidad: 5 cm

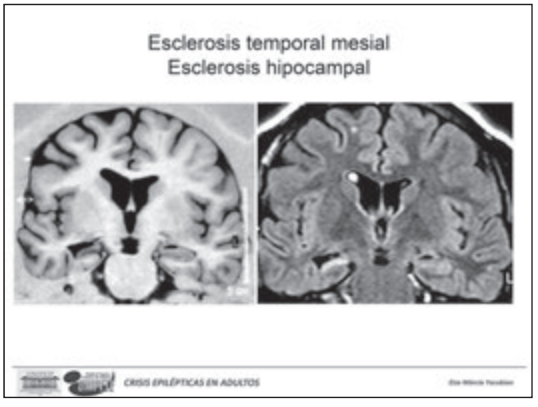


Jones, 1951
Pampiglione, 1956
Marshall, 1957




Fp1-F7
F7-Sp1
Sp1-T7
T7-P7
P7-O1
Fp2-F8
F8-Sp2
Sp2-T8
T8-P8
P8-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
CRISIS EPILÉPTICAS EN ADULTOS


Fp1-F7
F7-Sp1
Sp1-T7
T7-P7
P7-O1
Fp2-F8
F8-Sp2
Sp2-T8
T8-P8
P8-O2
Sp1-Sp2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
CRISIS EPILÉPTICAS EN ADULTOS


Esclerosis temporal mesial
Esclerosis hipocampal
CRISIS EPILÉPTICAS EN ADULTOS


Curso de la epilepsia relacionada con la esclerosis temporal mesial en 180 pacientes
Miyashira et al., 2004
EPI= 40.5%
Primera crisis espontánea 2-20 años
Refractariedad a FAE 28-48 años
Remisión 21% 12-20 años
Edad en la cirugía 30-48 años
0 4 8 12 16 20 24 28 32 36 40 44 48
Años
Media ± SD
CRISIS EPILÉPTICAS EN ADULTOS

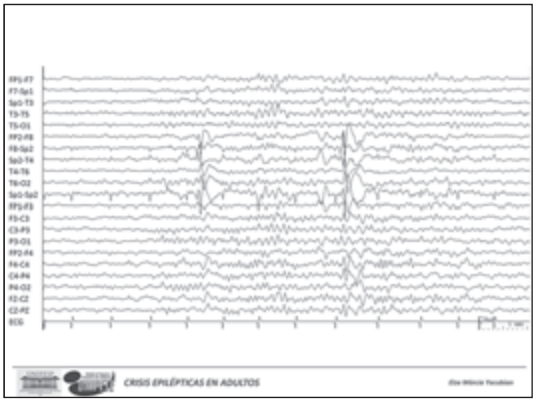
Mujer de 18 años de edad.

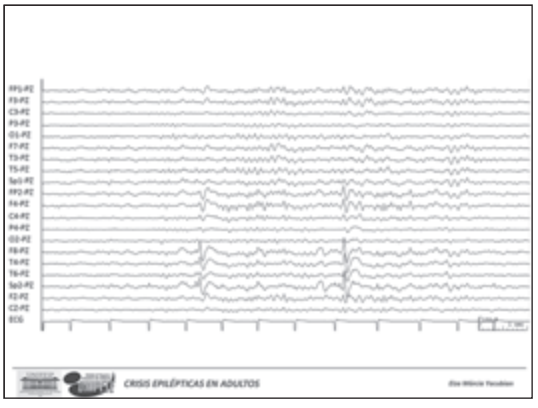
Historia de crisis febriles en la infancia.

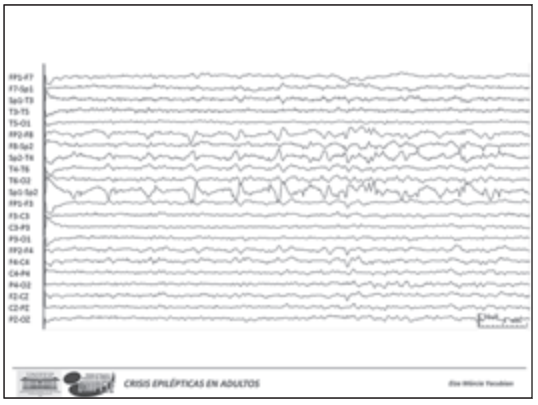
12 años: inicio de crisis recurrentes.

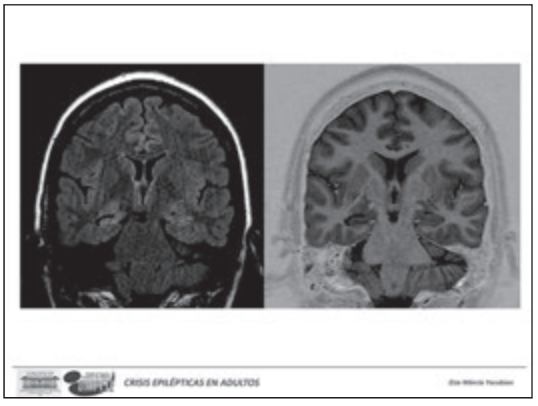
- aura: sensación de malestar epigástrico ascendiente
- crisis parciales complejas
  - ✓ detención del comportamiento
  - ✓ automatismos oraalimentares
  - ✓ *staring*
  - ✓ lenguaje incomprensible

***Caravaggio*, Medusa, 1592**
Uffizi, Firenza

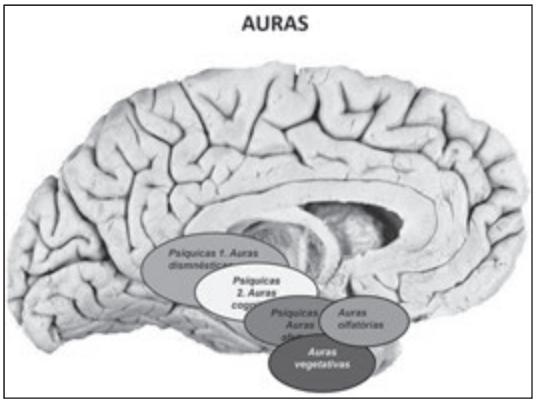


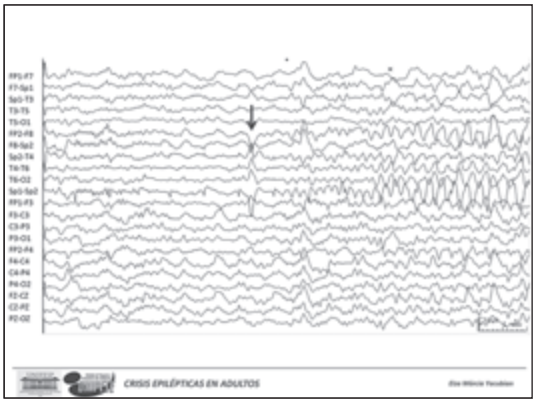


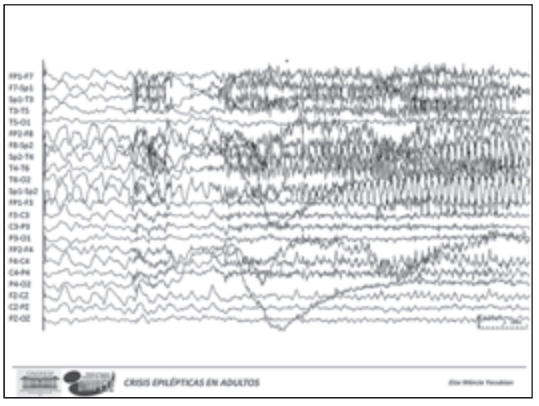

CRISIS EPILÉPTICAS EN ADULTOS

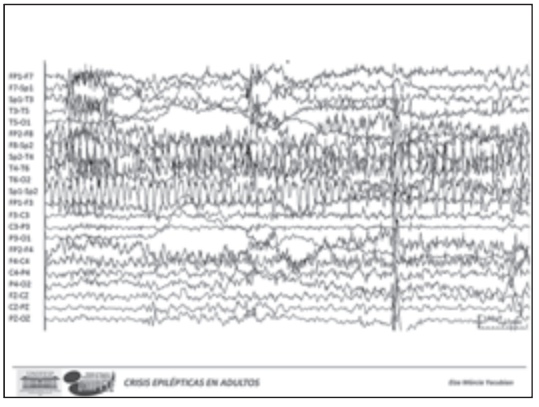

CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS


AURAS
Psíquicas 1. Auras
Psíquicas
2. Auras
Psíquicas
Auras
Auras
olfatorias
Auras
vegetativas


CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS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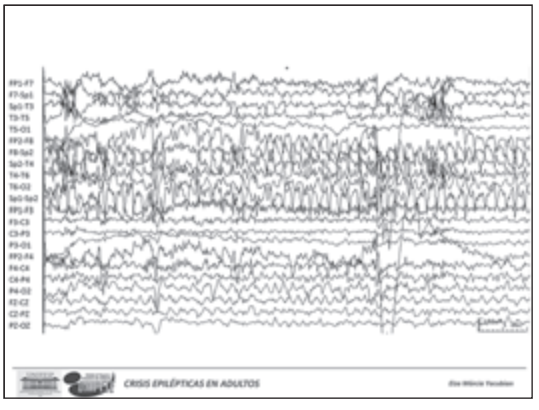
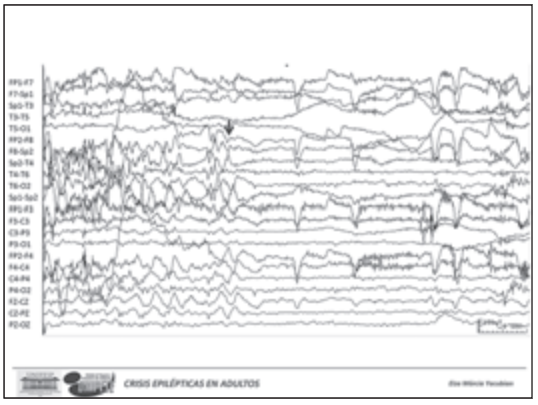
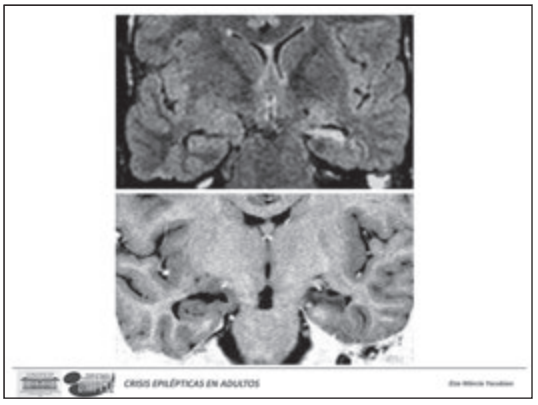

CRISIS EPILÉPTICAS EN ADULTOS

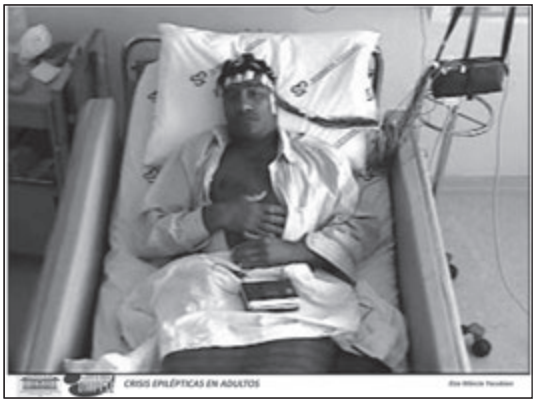


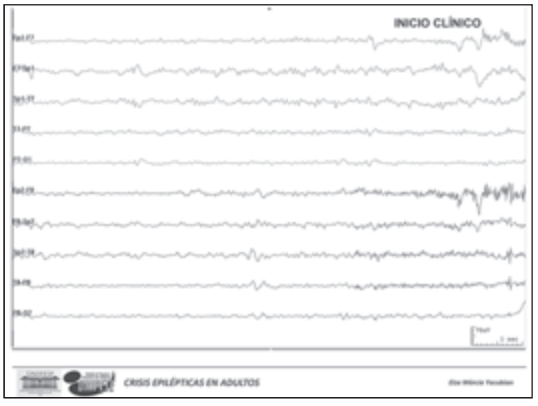
Hombre de 29 años de edad

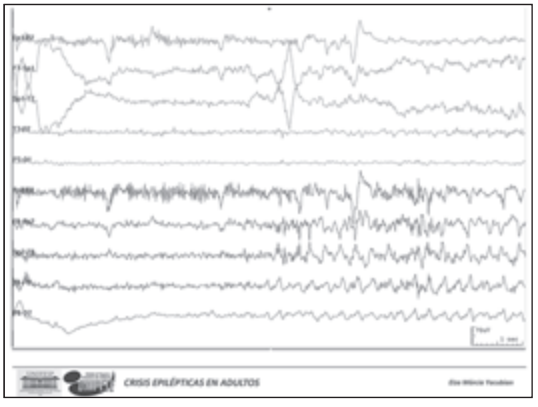
- 2 años: tuvo una crisis febril prolongada
- 8 años: crisis parciales complejas y CTCG
- 13 años: crisis usuales
  - ✓ aura abdominal
  - ✓ detención del comportamiento, staring
  - ✓ automatismos oroalimentares y gestuales
  - ✓ postura distónica: miembro superior derecho (?)
  - ✓ en algunas crisis: automatismo de escupir
  - ✓ pos-ictal: dificultad de hablar por 15 minutos
- crisis refractarias: 4-6 crisis/mes

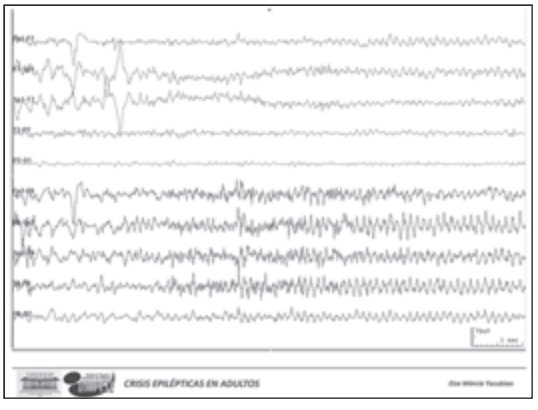
CRISIS EPILÉPTICAS EN ADULTOS

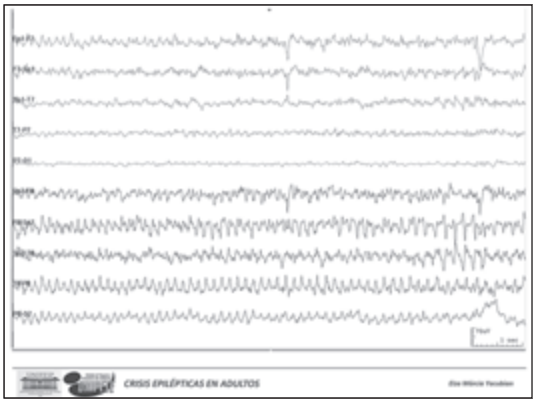



CRISIS EPILÉPTICAS EN ADULTOS


INICIO CLÍNICO
CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS



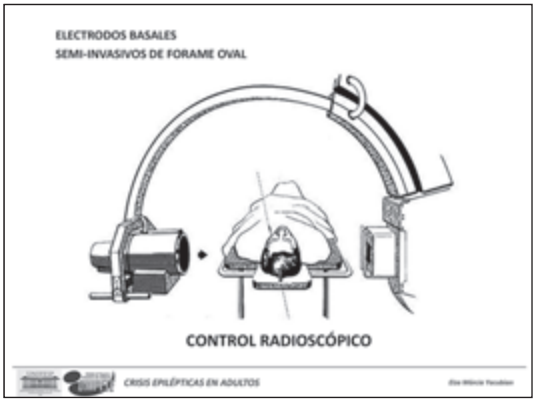
Datos discordantes:

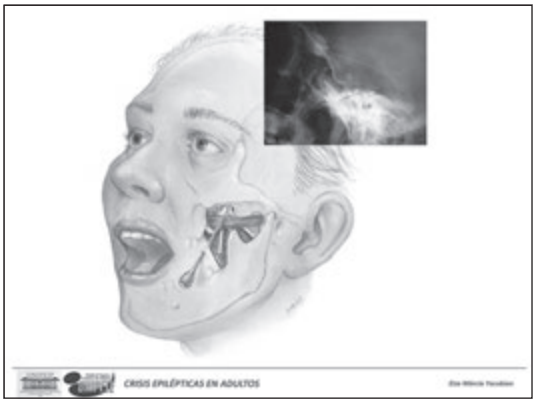
RM: esclerosis del hipocampo izquierdo

(hipocampo derecho normal)

x

Vídeo-EEG: crisis con inicio ictal en la región temporal derecha





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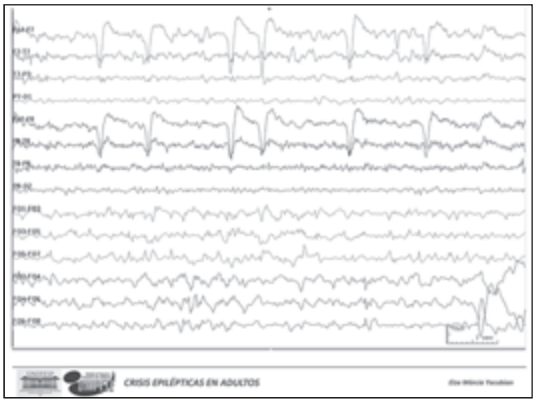

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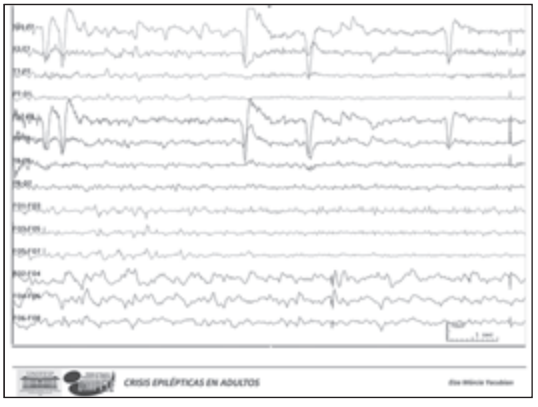

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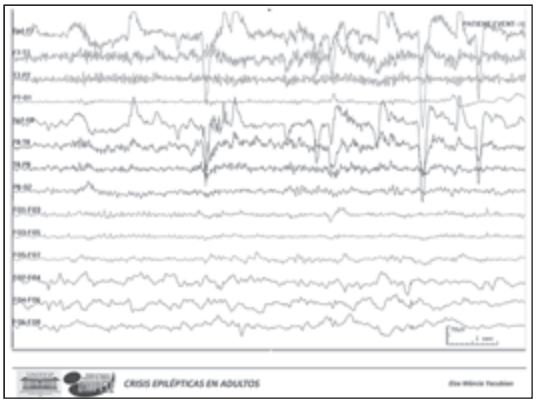
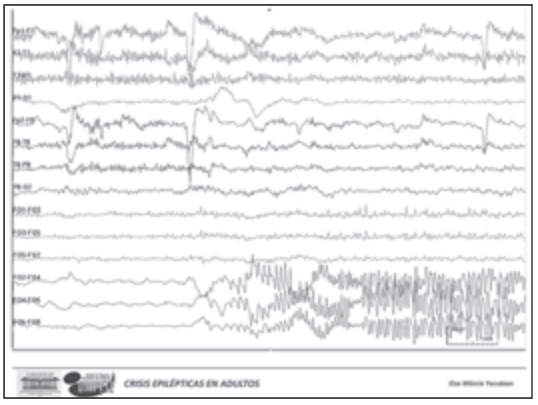
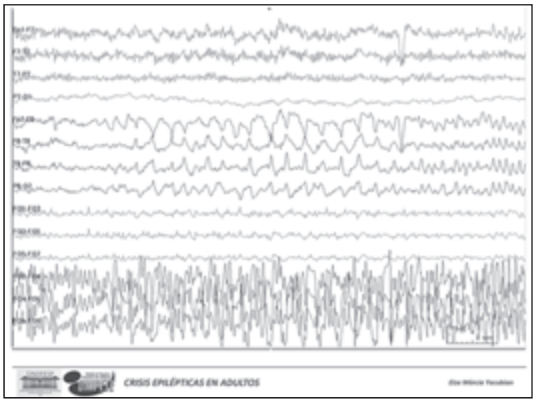
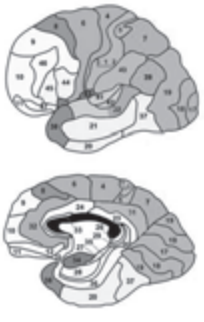


CRISIS EPILÉPTICAS EN ADULTOS



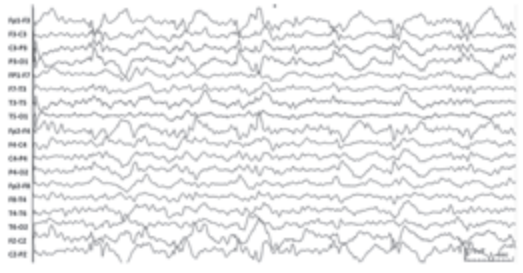


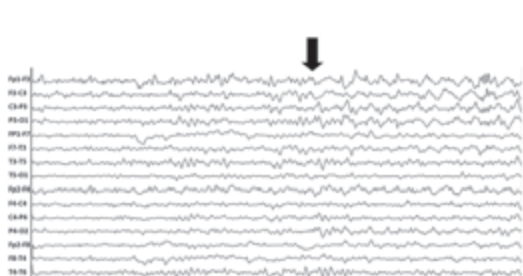
El lóbulo frontal

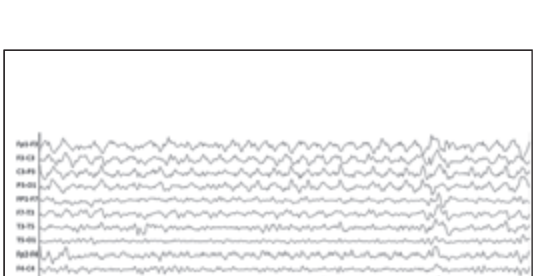


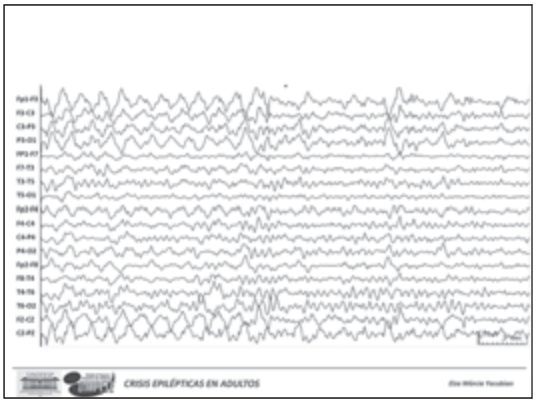
- **CORTEZA MOTORA:**
- **Lóbulo central:** áreas 4 y 3,1,2 de Brodmann
- **CORTEZA FRONTAL:**
- **Corteza pre-motora:**
  - **El área 6** (área sensorio-motora suplementaria)
  - **El área 8** (campo frontal de la mirada)
  - **Las áreas 44 y 45** (área motora del habla de Broca)
- **Corteza pre-frontal**

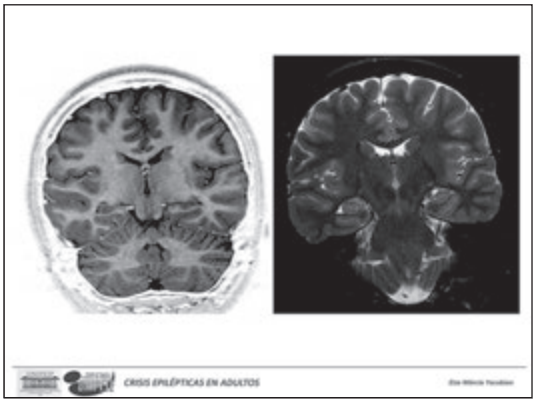
- Mujer de 22 años
- crisis epilépticas refractarias iniciadas a los 3 meses de vida
  - ✓ clonias afectando el hemicuerpo derecho
  - ✓ preservación de la consciencia
  - 3 a 5 crisis por semana, frecuentemente en salvas
- en ocasiones, ocurre generalización secundaria



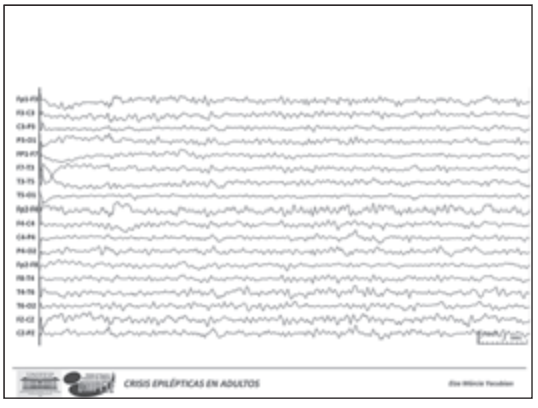





CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS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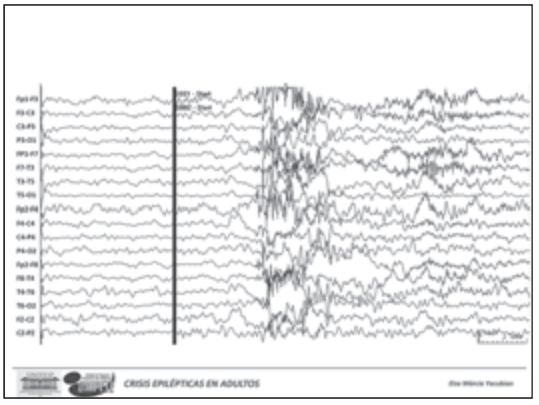
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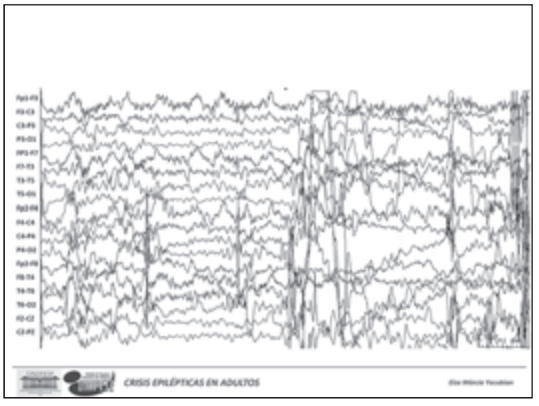
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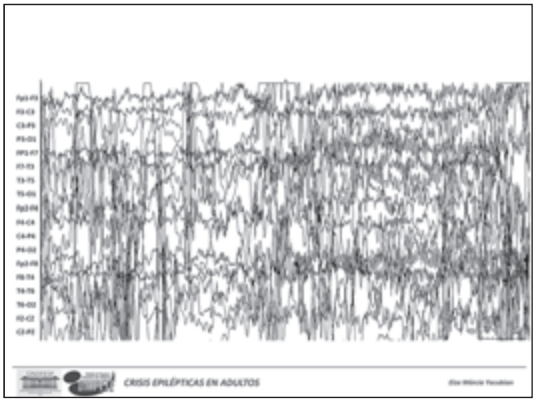
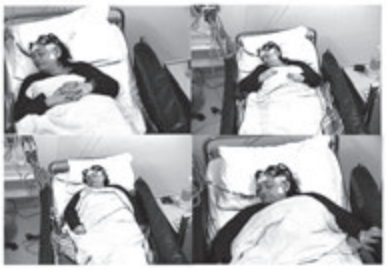
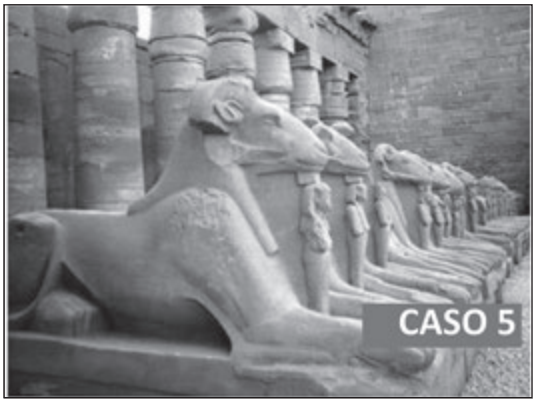

CRISIS EPILÉPTICAS EN ADULTOS


CASO 4

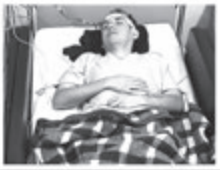
Características clínicas
Crisis del lóbulo frontal

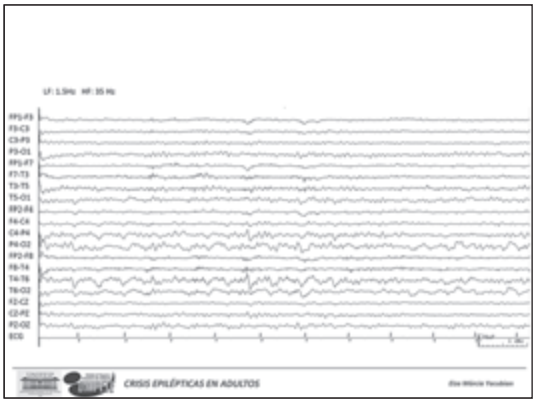
- **Eventos estereotipados**: el paciente le dirá que los eventos son siempre los mismos

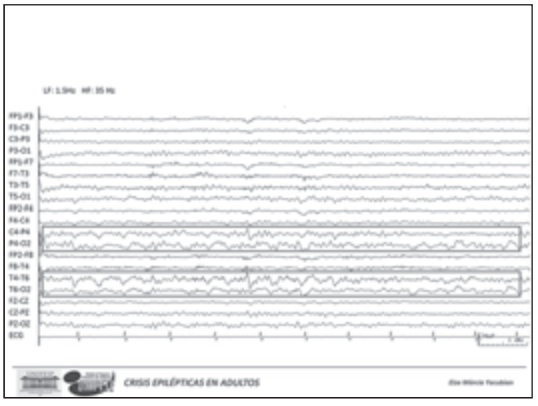




- EEG de hombre de 39 años
- historia de traumatismo cráneo encefálico (TCE) a los 6 meses de vida
- inicio de crisis epilépticas recurrentes a los 4 años
- aura: visión de "cometa naranja" en el campo visual izquierdo
- detención del comportamiento, staring y automatismos oroalimentarios
- duración de pocos minutos




LF: 1.5Hz HF: 35 Hz
CRISIS EPILÉPTICAS EN ADULTOS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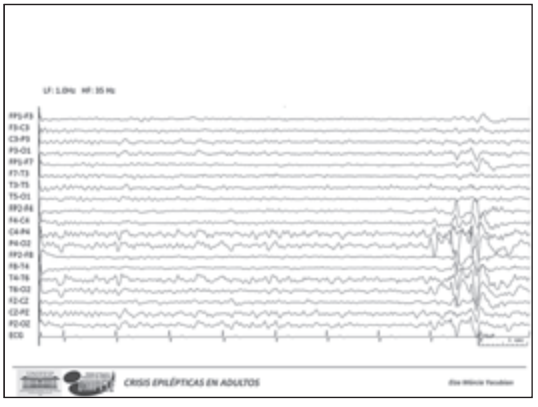
CRISIS EPILÉPTICAS EN ADULTOS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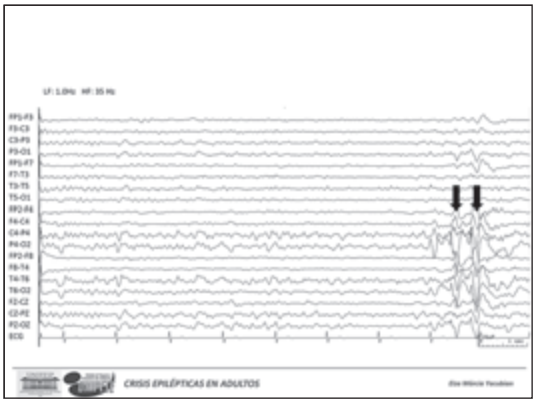
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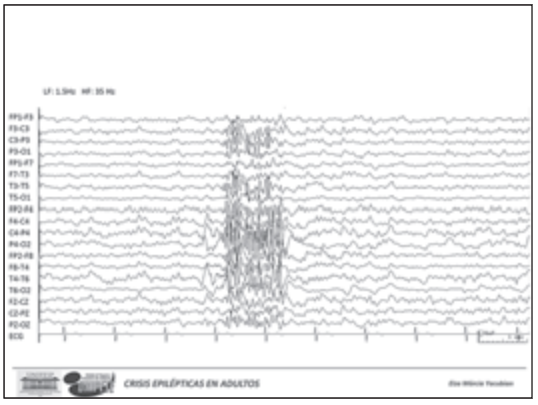
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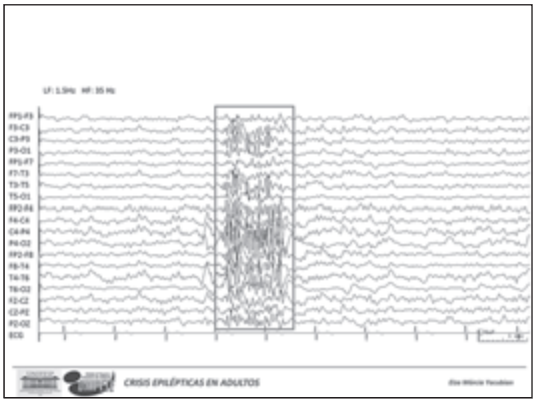
CRISIS EPILÉPTICAS EN ADULTOS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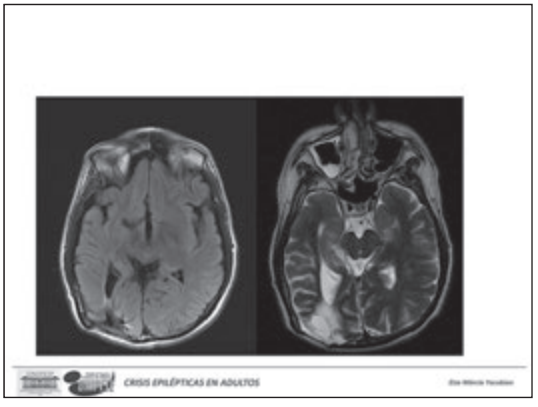
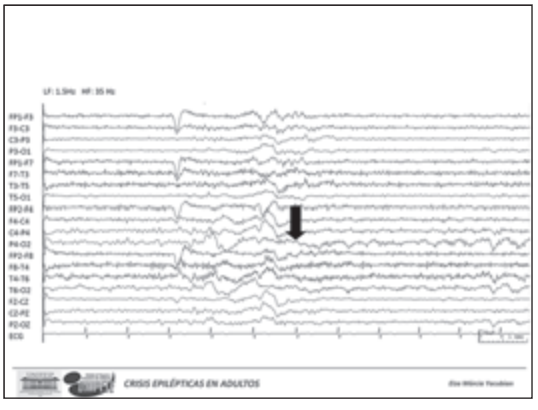
CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS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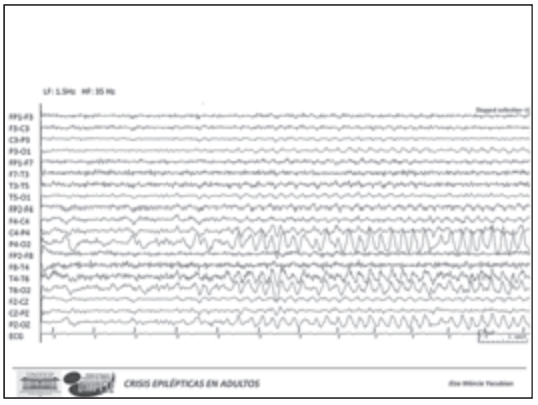
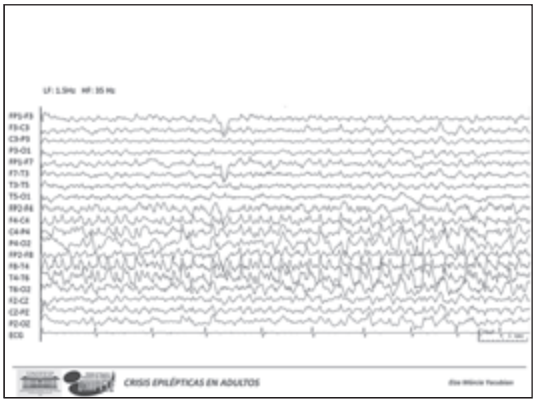
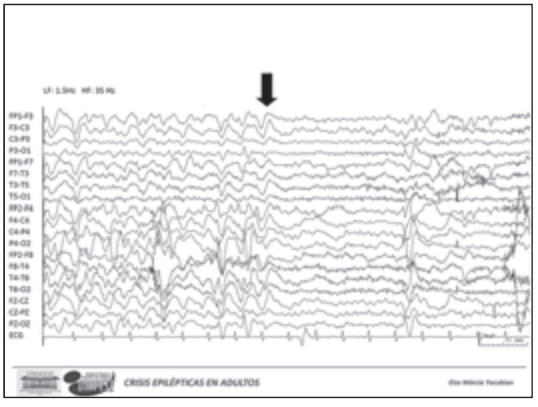
CRISIS EPILÉPTICAS EN ADULTOS







Clasificación de las crisis epilépticas

Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised clinical and electrographic classification of epileptic seizures ⇨ ILAE 1981 ***(Epilepsia 1981; 22: 489-501)***

Clasificación de los síndromes epilépticos

Commission on Classification and Terminology of the International League Against Epilepsy: Proposal for revised classification of epilepsies and epileptic syndromes ⇨ ILAE 1989 ***(Epilepsia 1989; 30: 389-399)***

CRISIS EPILÉPTICAS EN ADULTOS

ILAE – 1989

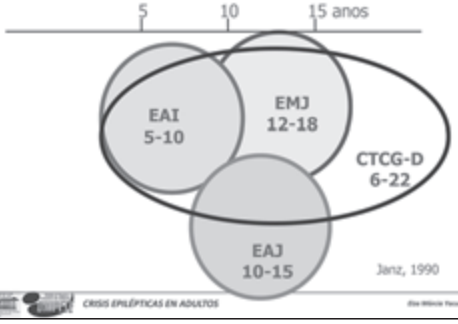
Proposal for revised classification of epilepsies and epileptic syndromes

1. **EPILEPSIAS y SÍNDROMES GENERALIZADAS**

2.1 Idiopáticas, relacionadas a edad

- Epilepsia con ausencias juvenil
- Epilepsia mioclónica juvenil
- Epilepsia com crisis tónico-clónicas generalizadas

Edad de inicio y síndromes y superposición de las EGI de la infancia y la adolescencia



Lo que tienen en común?

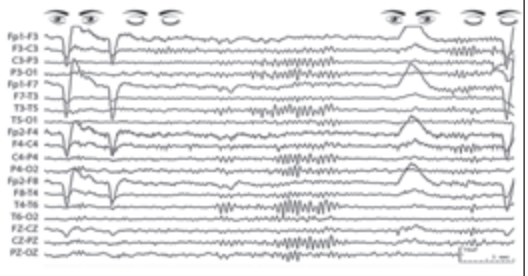
- La combinación, en proporciones diferentes, de tres tipos de crisis: ausencias, crisis tónico-clónicas generalizadas y crisis mioclónicas
- El momento de la crisis: el despertar relacionadas, temprano por la mañana y relajación en la tarde o al anochecer
- Factores precipitantes de las crisis:
  - Privacion de sueño
  - Consumo excesivo de alcohol
  - Estrés
  - Menstruación

Epilepsia con ausencias juvenil

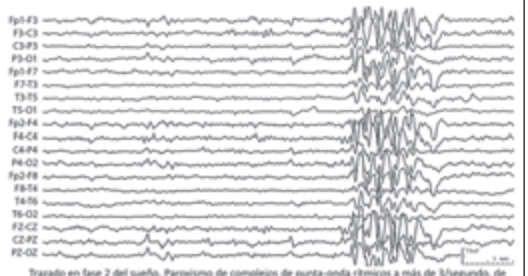
Espaniolepsia- de lo griego σπάνιο, raro

Epilepsia con ausencias juvenil

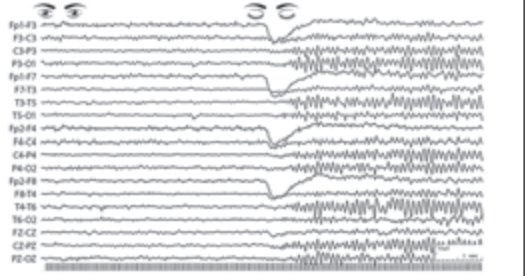
- Las crisis de ausencias son las mismas que se observan en la epilepsia con ausencias de la infancia
- Ocurre por igual en ambos los sexos
- El inicio ocurre alrededor de la pubertad
- La frecuencia de las crisis es más baja que en la picnolepsia y las ausencias no son diarias
- La mayoría de las crisis ocurre esporádicamente
- La asociación con crisis generalizadas tónico-clónicas es frecuente, pudiendo ser precedidas por ausencias
- Es frecuente que los pacientes presenten crisis mioclónicas



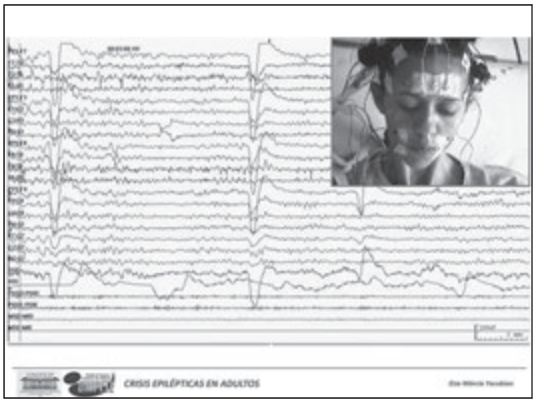
EEG en vigilia. Actividad de base normal



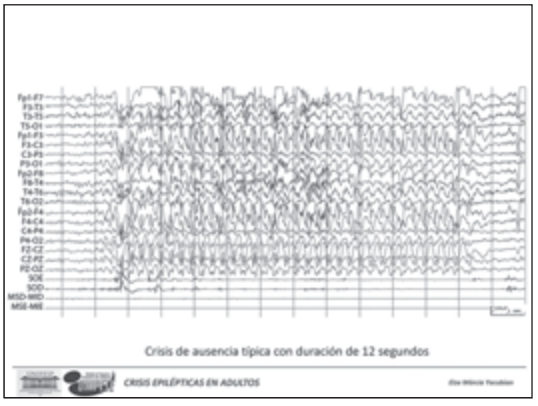
Trazado en fase 2 del sueño. Paroxismo de complejos de punta-onda rítmicos a más de 3/segundo, de proyección difusa y bilateral, predominando en regiones anteriores



Ausencia de fotosensibilidad



CRISIS EPILÉPTICAS EN ADULTOS



Crisis de ausencia típica con duración de 12 segundos

CRISIS EPILÉPTICAS EN ADULTOS

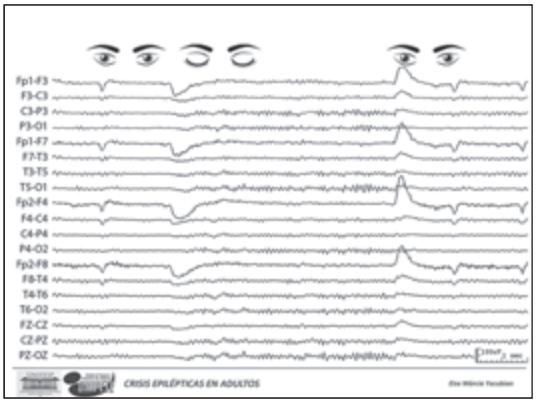
Epilepsia mioclónica juvenil

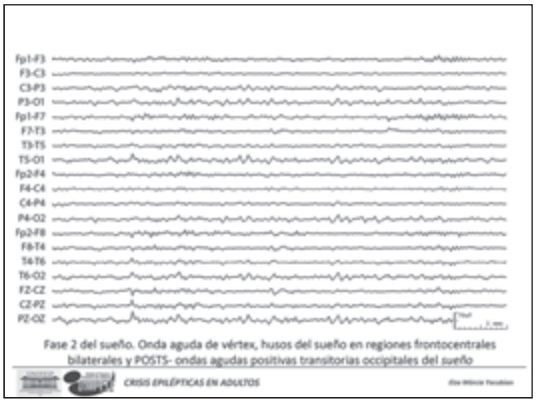
CRISIS EPILÉPTICAS EN ADULTOS

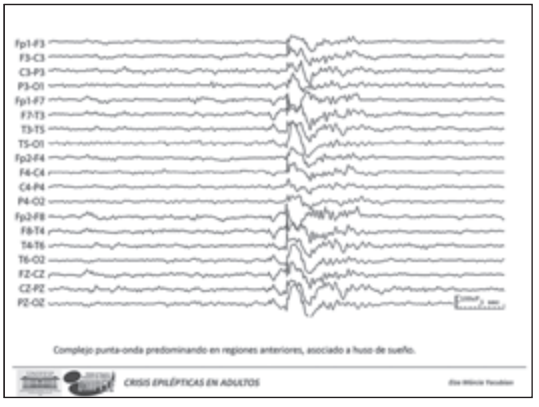
Epilepsia mioclónica juvenil
Criterios diagnósticos-2011

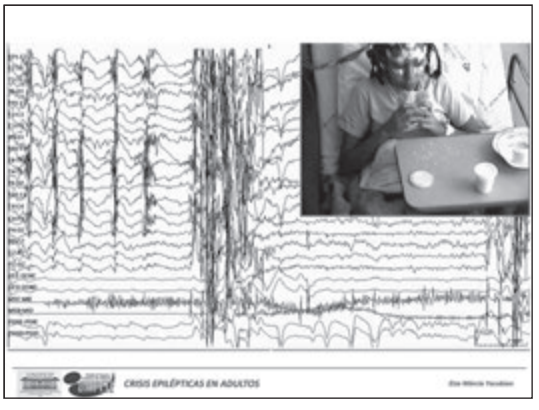
- **Clase I** comprende: 1.sacudidas mioclónicas acompañando las anormalidades del EEG; 2. mioclonías sin pérdida de consciencia ocurriendo exclusivamente por la mañana hasta 2 horas después del despertar; 3. edad de inicio entre 10 y 25 años;
- **Clase II**: Los criterios son más amplios. Admite: 1. mioclonías predominantemente después del despertar; 2. una franja de edad de inicio mayor (6-25 años); 3. anormalidades EEG epileptiformes con o sin sacudidas mioclónicas concomitantes

CRISIS EPILÉPTICAS EN ADULTOS

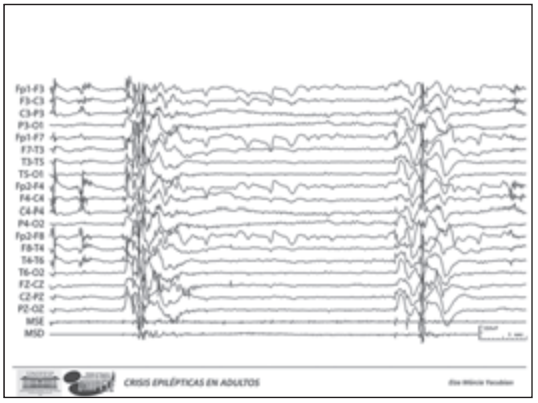

Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
PZ-OZ
CRISIS EPILÉPTICAS EN ADULTOS


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
PZ-OZ
Fase 2 del sueño. Onda aguda de vértex, husos del sueño en regiones frontocentrales bilaterales y POSTS- ondas agudas positivas transitorias occipitales del sueño
CRISIS EPILÉPTICAS EN ADULTOS


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
FZ-CZ
CZ-PZ
PZ-OZ
Complejo punta-onda predominando en regiones anteriores, asociado a huso de sueño.
CRISIS EPILÉPTICAS EN ADULTOS


CRISIS EPILÉPTICAS EN ADULTOS

Epilepsia com crisis tónico-clónicas generalizadas



MUCHAS GRACIAS!

Tonicarlo Velasco (Brazil)

SEIZURES IN THE ELDERLY

João Malva (Portugal)

NEURONAL DEATH: DIFFERENT PATHS TO THE SAME FATE

Catarina Oliveira (Portugal)

OXIDATIVE STRESS AND NEURONAL CELL DEATH

LASSE VIII
"Epilepsy in Neurodegenerative diseases and Aging"
17th February, 2014

Oxidative Stress and Neuronal Cell Death

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CNC-Center for Neuoscience and Cell Biology
Faculty of Medicine, University of Coimbra, Portugal

CNC

Outline

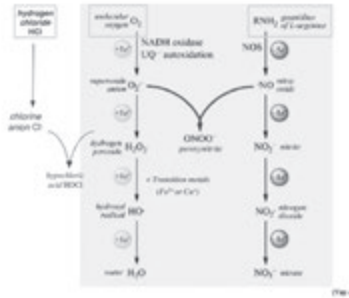
- Oxidative Stress current view
- Reactive Oxygen Species: intracellular sources and targets
- Redox signalling in cell death versus cell survival decision
- Biological consequences of oxidative stress
  - Proteosome and autophagy impairement
- Oxidative stress and neurodegeneration
  - Alzheimer's disease as a paradigm
- Oxidative stress and epileptogenesis

Oxidative stress

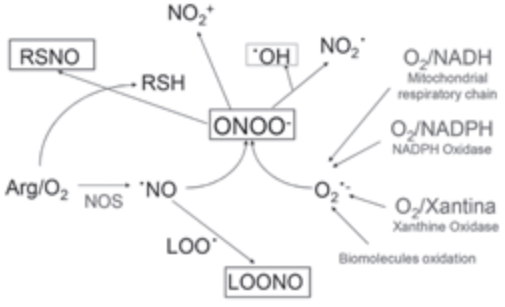
1. **Classically:** unbalance between production of ROS/RNS and antioxidants.
2. **Currently:** Altered redox signaling and control resulting from oxidant insult.

Oxidative Stress

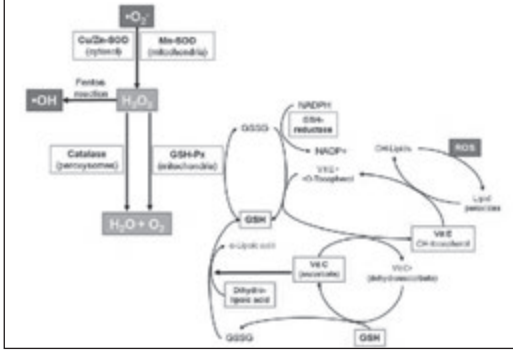
Reactive oxygen (ROS), nitrogen (RNS) and chlorine species formation



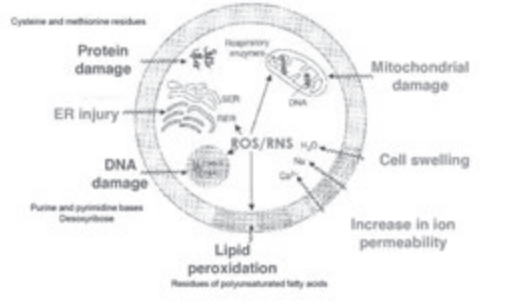
ROS and RNS interplay



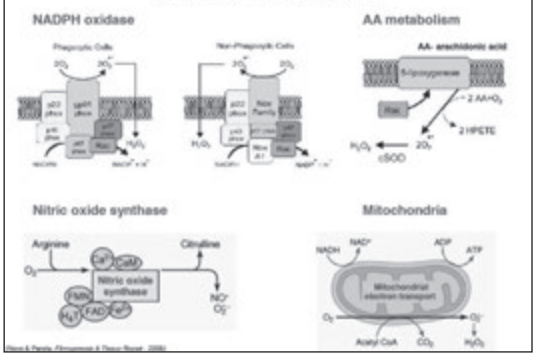
Redox balance:ROS/antioxidants



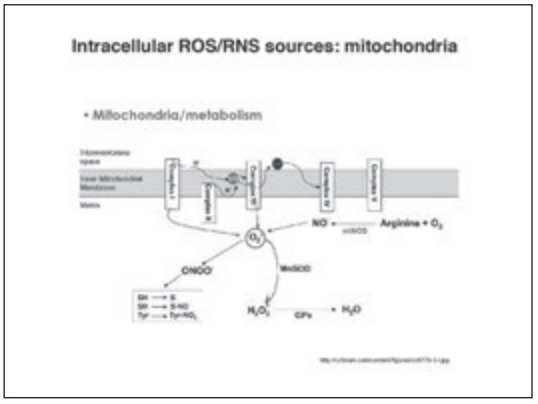
Cellular targets of ROS/RNS



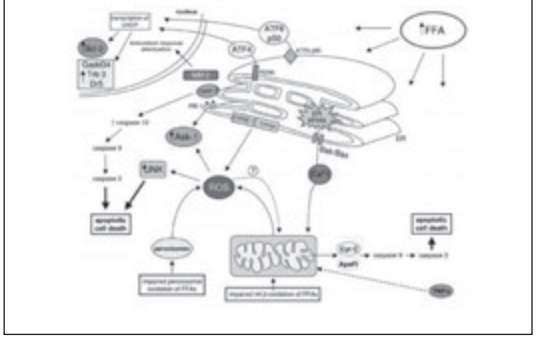
Main sources of ROS/RNS



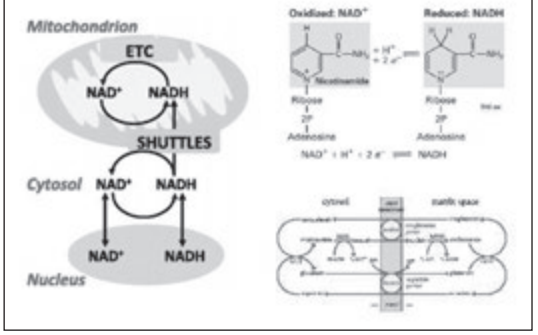
Intracellular ROS/RNS sources: mitochondria

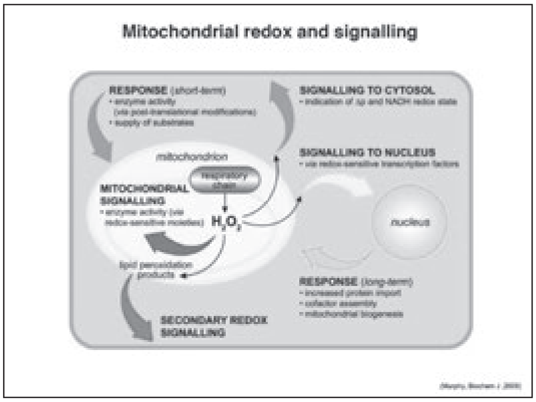


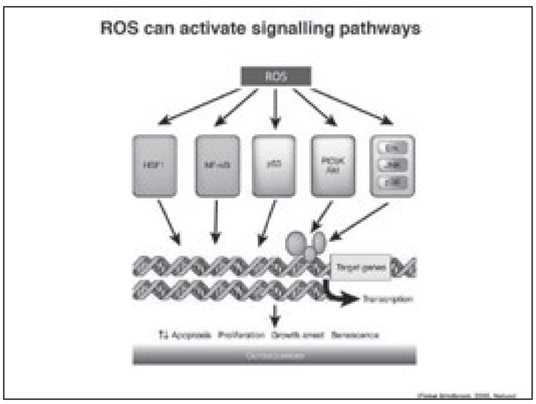
Intracellular ROS/RNS sources: endoplasmic reticulum (ER)

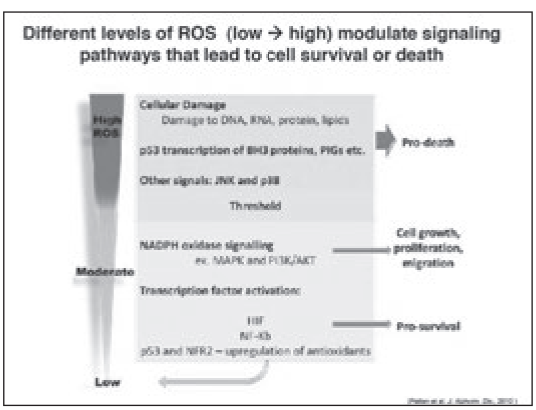


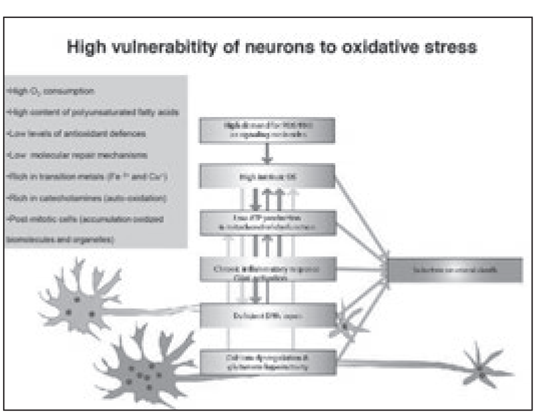
NAD+/NADH ratio



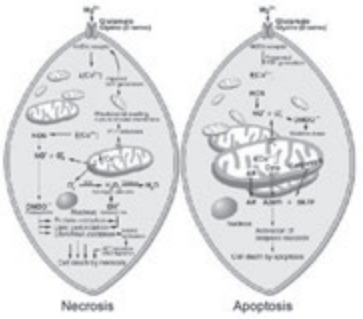

Mitochondrial redox and signalling
RESPONSE (short-term)
• enzyme activity (via post-translational modifications)
• supply of substrates
SIGNALLING TO CYTOSOL
• indication of Δp and NADH redox state
mitochondrion
respiratory chain
SIGNALLING TO NUCLEUS
• via redox-sensitive transcription factors
MITOCHONDRIAL SIGNALLING
• enzyme activity (via redox-sensitive moieties)
H2O2
nucleus
lipid peroxidation products
RESPONSE (long-term)
• increased protein import
• cofactor assembly
• mitochondrial biogenesis
SECONDARY REDOX SIGNALLING


ROS can activate signalling pathways
ROS
HSF1
NF-κB
p53
PI3K Akt
Target genes
Transcription
Apoptosis Proliferation Growth arrest Senescence

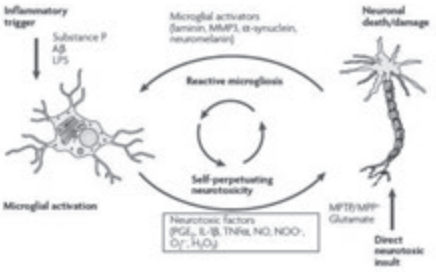

Different levels of ROS (low → high) modulate signaling pathways that lead to cell survival or death
High ROS
Cellular Damage
Damage to DNA, RNA, protein, lipids
p53 transcription of BH3 proteins, PIGs etc.
Pro-death
Other signals: JNK and p38
Threshold
NADPH oxidase signalling
ex. MAPK and PI3K/AKT
Cell growth, proliferation, migration
Moderate
Transcription factor activation:
HIF
NF-Kb
p53 and NFR2 – upregulation of antioxidants
Pro-survival
Low


High vulnerabitity of neurons to oxidative stress
•High O2 consumption
•High content of polyunsaturated fatty acids
•Low levels of antioxidant defences
•Low molecular repair mechanisms
•Rich in transition metals (Fe and Cu)
•Rich in catecholamines (auto-oxidation)
•Post mitotic cells (accumulation oxidized biomolecules and organelles)

ROS can activate apoptosis and necrosis pathways

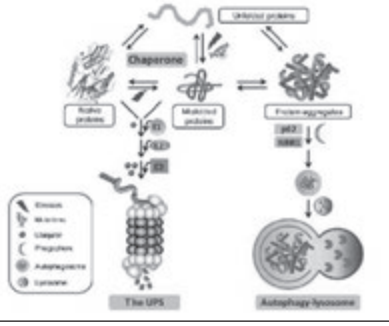


Neuroinflammation- a cause and consequence of ROS

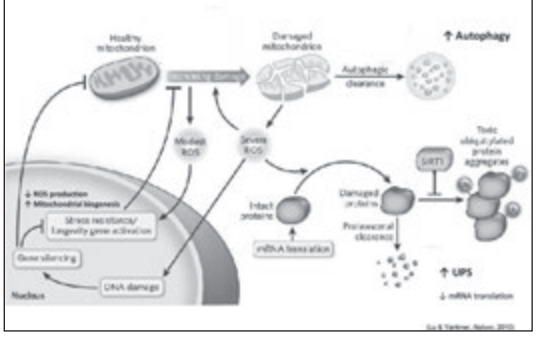


Biological consequences of oxidative stress

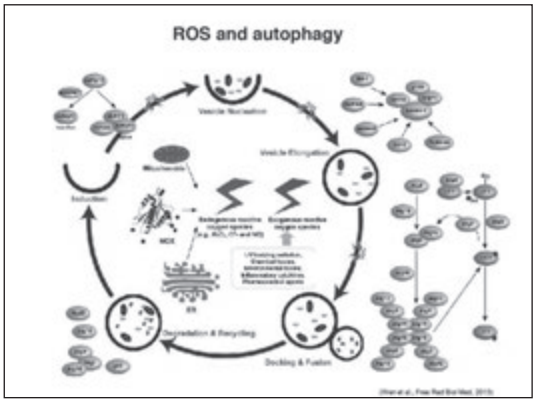
Misfolded proteins:- a consequence of oxidative stress

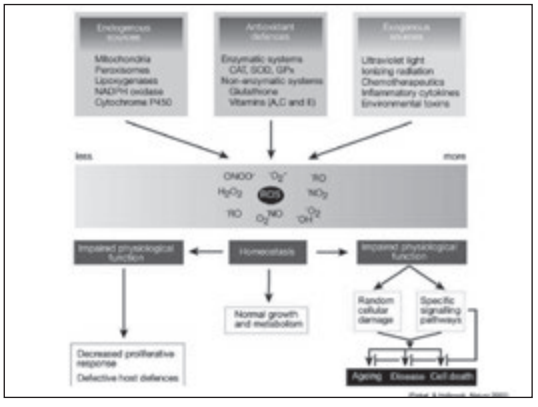


Proteasome and autophagy impairment

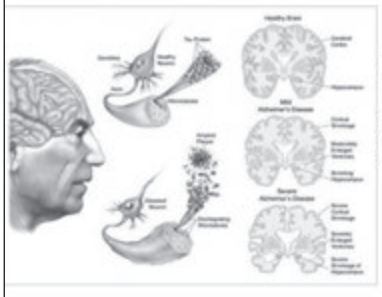


ROS and autophagy



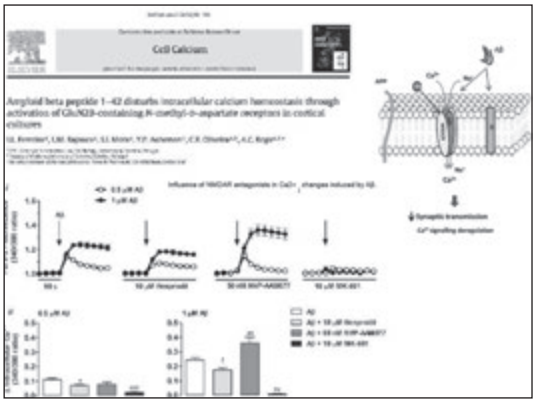


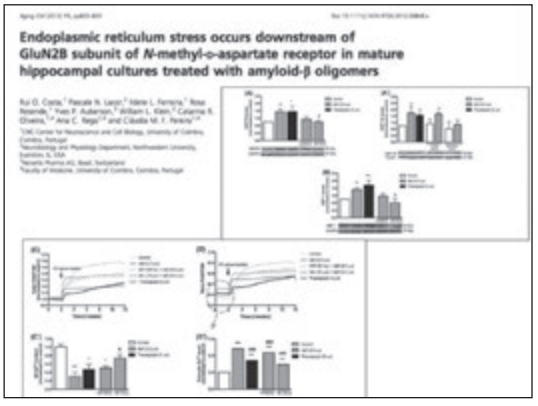
Oxidative stress in Alzheimer´s disease

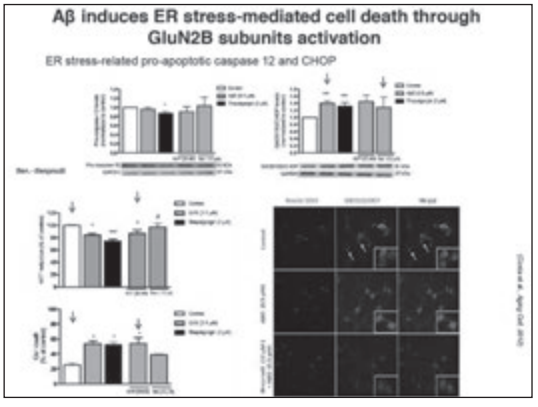


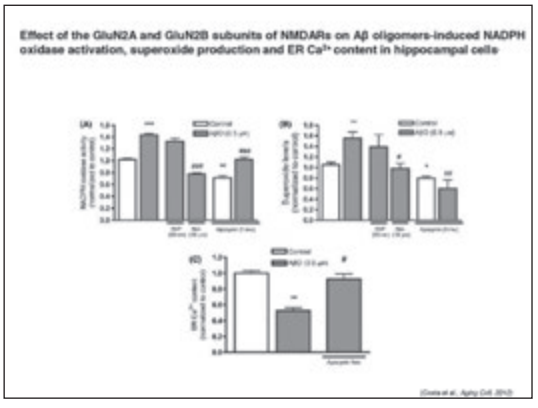
Cognitive and Memory Deficits

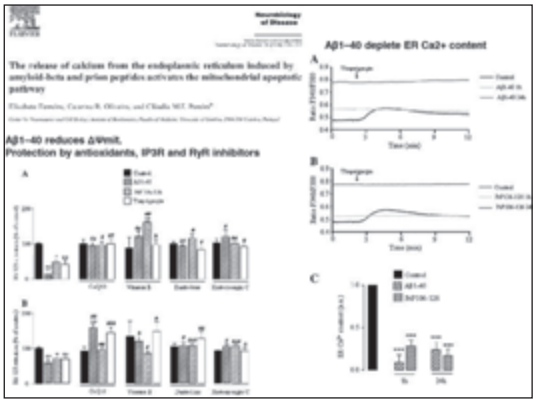
- Amyloid-beta accumulation
- Tau hyperphosphorylation
- Synaptic and neuronal loss

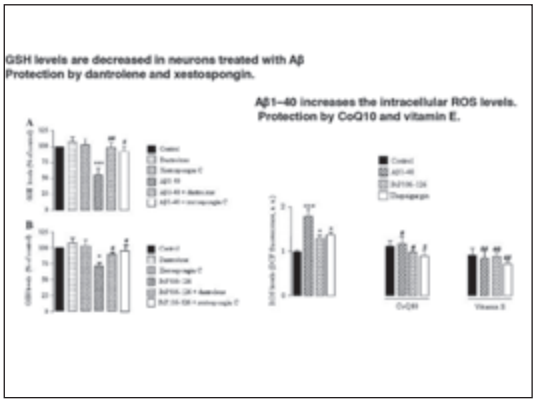

Cell Calcium
Amyloid beta peptide 1–42 disturbs intracellular calcium homeostasis through activation of GluN2B-containing N-methyl-D-aspartate receptors in cortical cultures

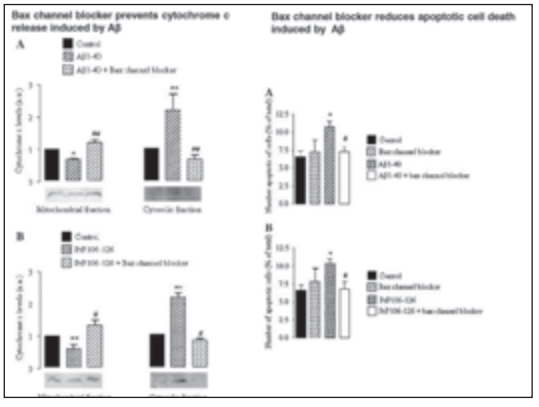

Endoplasmic reticulum stress occurs downstream of GluN2B subunit of N-methyl-D-aspartate receptor in mature hippocampal cultures treated with amyloid-β oligomers

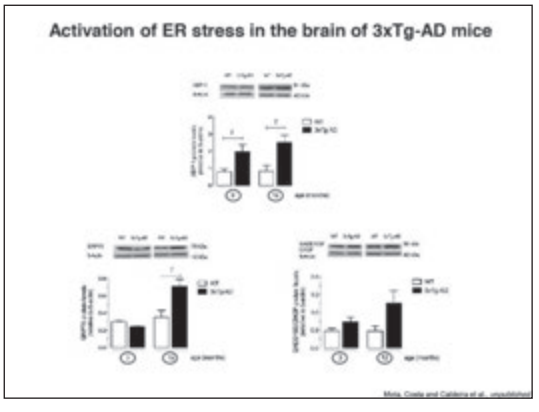

Aβ induces ER stress-mediated cell death through GluN2B subunits activation
ER stress-related pro-apoptotic caspase 12 and CHOP


Effect of the GluN2A and GluN2B subunits of NMDARs on Aβ oligomers-induced NADPH oxidase activation, superoxide production and ER Ca2+ content in hippocampal cells

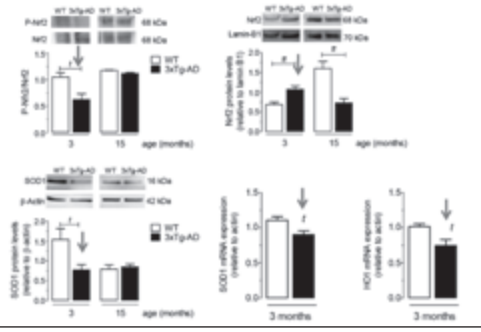

Neurobiology of Disease
The release of calcium from the endoplasmic reticulum induced by amyloid-beta and prion peptides activates the mitochondrial apoptotic pathway
Aβ1–40 deplete ER Ca2+ content
Aβ1–40 reduces ΔΨmit.
Protection by antioxidants, IP3R and RyR inhibitors


GSH levels are decreased in neurons treated with Aβ
Protection by dantrolene and xestospongin.
Aβ1–40 increases the intracellular ROS levels.
Protection by CoQ10 and vitamin E.

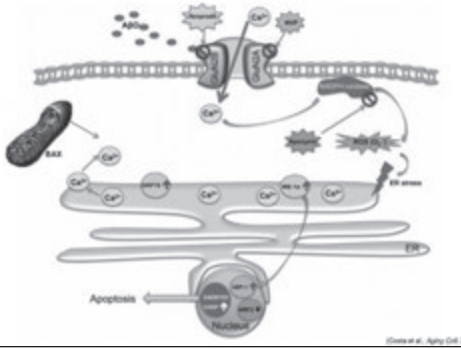

Bax channel blocker prevents cytochrome c release induced by Aβ
Bax channel blocker reduces apoptotic cell death induced by Aβ


Activation of ER stress in the brain of 3xTg-AD mice

Decreased nuclear Nrf2 activation in young 3xTg-AD mice cortex appears to underlie reduced SOD1 and HO1 mRNA levels



Summary of NMDAR-dependent Aβ neurotoxicity

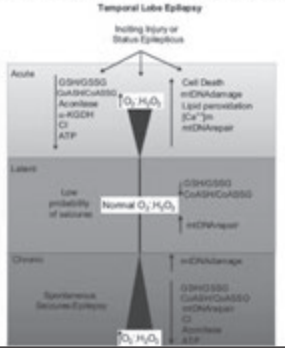


Oxidative Stress and Brain Disorders

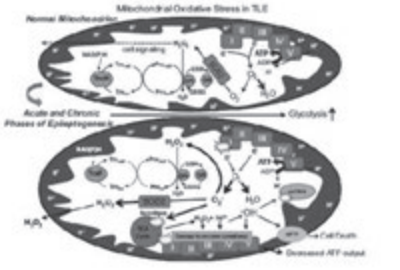
Some brain disorders involve free radical generation	
Parkinson's disease	Dementia
Alzheimer's disease	Down's syndrome
Stroke	Progeria
Epileptic seizures	Werner's syndrome
Head trauma	Shock
Retinal damage	Brain edema
Multiple sclerosis	Tardive dyskinesia
Schizophrenia	Huntington's disease
Aging	

Acute *vs* chronic diseases

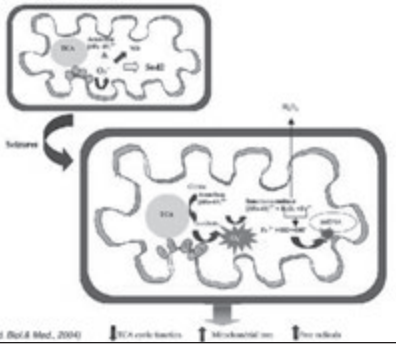
Mitochondrial oxidative stress during the acute, latent and chronic phases of epileptogenesis.



Mitochondrial oxidative stress in acute and chronic phases of Epileptogenesis

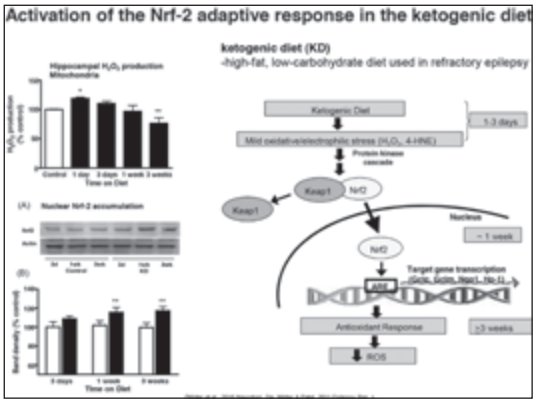


Seizure-induced mitochondrial $O_2^{\cdot-}$ toxicity via oxidative aconitase inactivation.

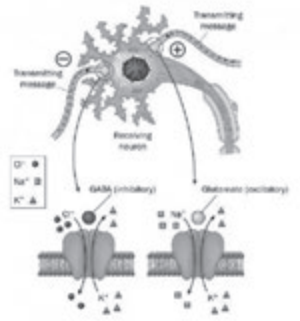


Mechanisms of cell damage in Epilepsy

Activation of the Nrf-2 adaptive response in the ketogenic diet

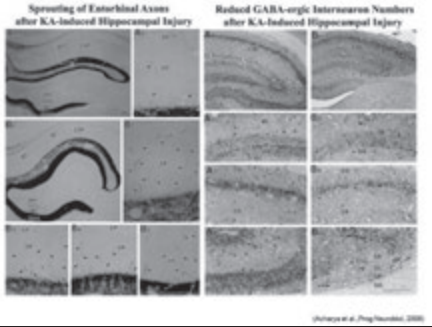


Neurotransmission is affected in Epilepsy



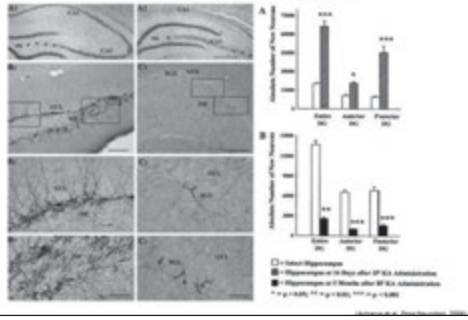
Neural circuits are affected in Epilepsy

KA- Kainic acid model



Neural circuits are affected in Epilepsy

Enhanced Production and Abnormal Migration of New Granule Cells into the Dentate Hilus after KA-induced Status Epilepticus



João Malva (Portugal)

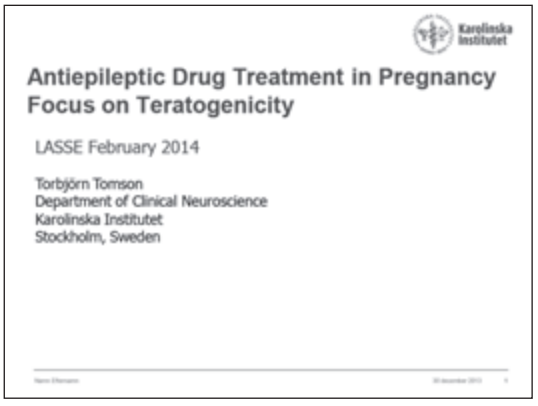
EXCITOTOXICITY: GLUTAMATE OUT OF THE CAGE

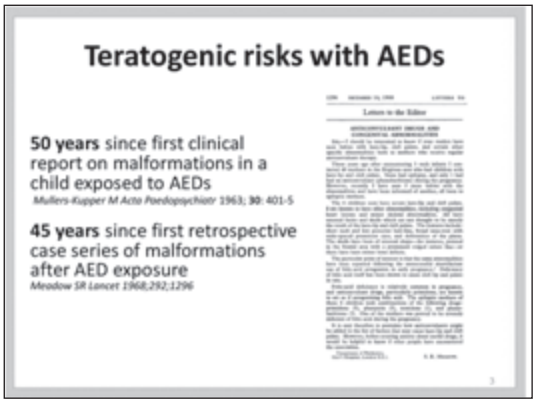
Joana Palha (Portugal)

BRAIN BARRIERS I

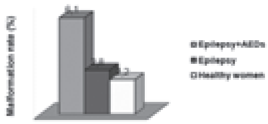
Torbjorn Tomson (Sweden)

ANTIEPILEPTIC DRUG TREATMENT IN PREGNANCY WITH FOCUS IN TERATOGENICITY





Increased risk mainly related to use of AEDs



From Tomson and Battino. The management of epilepsy in pregnancy. In Shorvon, Pedley (eds) Blue Books of Neurology. The Epilepsies 3, Butterworth, Heinemann, Philadelphia, PA, 2009

Fetal and Maternal Risks with Uncontrolled Seizures

- **Fetal risks**
  - Generalized tonic-clonic seizures (GTCS) can induce foetal hypoxia/acidosis [2]
  - GTCS during delivery reduce foetal heart [3]
  - Risk of foetal loss in GTC-status [4]
  - Risk of traumatic foetal injury with maternal seizures
  - 5 or more GTCS during pregnancy associated with lower verbal IQ in the offspring [1]
- **Maternal risks**
  - Usual social, medical and psychological effects
  - Epilepsy accounts for 3.8%-5.4% of all maternal deaths in the UK [1,5]

1 Adab N, et al. J Neurol Neurosurg Psychiatry 2004;75:1575-832. Hiilesmaa eta al Am J Obstet Gynecol 1985;152:499-504. ; 3 Teramo et al., J Perinat Med 1979;7:3-6;4EURAP Study Group. Neurology 2006;66:354-60;* , Cantwell et al BJOG 2011

Maternal risks with uncontrolled seizures

Maternal deaths in UK 1985-1999 *Adab et al., JNNP 2004*

Maternities	11.26 million
Direct & indirect deaths	1199
Deaths/Maternities	0.01%
Deaths in epilepsy	46
Deaths in epilepsy/All deaths	3.8%

Maternal deaths in UK 2006-2008

Cantwell et al BJOG 2011

- 261 maternal deaths in total
- 14 died of epilepsy (5.4%)
- 11/14 classified as SUDEP

Most women maintain their seizure control during pregnancy

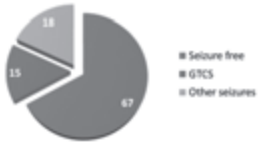
Prospective data from EURAP

EURAP Study Group Neurology 2006

FULL-LENGTH ORIGINAL RESEARCH

Seizure control and treatment changes in pregnancy: Observations from the EURAP epilepsy pregnancy registry

3,806 pregnancies with monotherapy
CBZ, LTG, VPA, PB



Treatment of Epilepsy in Pregnancy
The Aim

- Prevention of major convulsive seizures (GTCS) during pregnancy
- Minimized exposure of foetus to potentially teratogenic drugs

Higher risk with polytherapy

Table 3. Rates of occurrence of malformation-bearing pregnancies in 14 published series, with a comparison of the RR of each pregnancy in AED polytherapy-treated women as compared with their monotherapy-treated counterparts

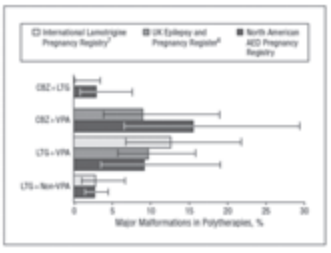
Author	Malformation rate n % (no. of pregnancies)		Poly- versus monotherapy	
	≥1 AED	1 AED	Relative risk	95% CI
Druzen et al. (1992)	15.8 (129)	5.0 (1.89)	3.09	1.45–6.62*
Wide et al. (2004)	4.3 (143)	1.6 (1.256)	3.63	1.08–6.59*
Dean et al. (2002)	20.5 (51)	11.0 (210)	3.33	1.27–6.27*
Cunnington et al. (2003)	13.5 (68)	2.9 (414)	2.04	0.98–4.35
Richmond et al. (2004)	9.1 (77)	4.5 (238)	1.95	0.80–4.79
Kaaja et al. (2003)	6.2 (146)	3.2 (594)	1.93	0.89–4.17
Morrow et al. (2006)	6.0 (718)	3.7 (2,468)	1.62	1.14–2.31*
Kaneko et al. (1999)	10.7 (385)	7.8 (508)	1.37	0.90–2.07
Holmes et al. (2001)	28.0 (129)	20.6 (210)	1.36	0.89–2.05
Samrén et al. (1997)	9.8 (312)	8.0 (709)	1.21	0.85–1.75
Canger et al. (1999)	5.3 (114)	3.7 (513)	0.92	0.37–2.25
Diav-Citrin et al. (2001)	6.1 (49)	6.6 (91)	0.92	0.24–3.51
Kaneko et al. (1992)	5.5 (163)	6.0 (116)	0.91	0.35–2.39
Australian 1 month	3.9 (382)	5.2 (791)	0.75	0.29–1.66
Australian 1 year	5.3	7.8	0.68	0.29–1.17

Studies are listed in descending order of relative risk.
AED, antiepileptic drug; CI, confidence interval; RR, relative risk.

Vajda et al. Epilepsia 2010;51:805-810

Fetal Effects of Anticonvulsant Polytherapies

All polytherapies are not equal

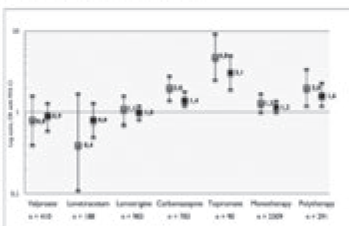


Arch Neurol. Published online June 13, 2011. doi:10.1001/archneurol.2011.133

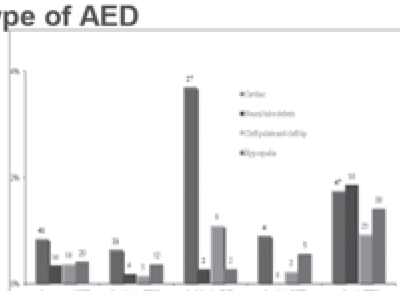
Factors to consider in selection of AEDs for women of childbearing age

- Relative teratogenic potential
  - →Intrauterine growth retardation
  - →major congenital malformations
  - →effects on cognitive development and behaviour
- Effectiveness in controlling seizures
  - →-effectiveness vs. type of epilepsy
  - →-specifically in pregnancy (PK changes)

Growth restrictions



Malformations profiles vary with type of AED



Tomson & Battino Lancet Neurol 2012

Overall Rates of MCM by AED monotherapy in different registries

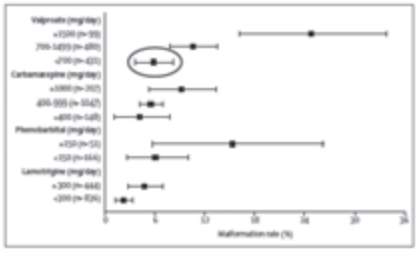
	Valproate	Carbamazepine	Lamotrigine	Phenobarbital	Phenytoin
International Lamotrigine Pregnancy Registry*	-	-	[illegible]	-	-
Finnish Medical Birth Registry and drug prescription databases*	[illegible]	[illegible]	-	-	[illegible]
Swedish Medical Birth Registry*	[illegible]	[illegible]	[illegible]	-	[illegible]
UK Epilepsy and Pregnancy Register*	[illegible]	[illegible]	[illegible]	-	[illegible]
North American AED Pregnancy Registry*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
International Registry of Antiepileptic Drugs and Pregnancy (EURAP)*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 1: Rates of major congenital malformations in six different studies

Tomson and Battino Lancet Neurol 2012

Is the risk dose-dependent? EURAP

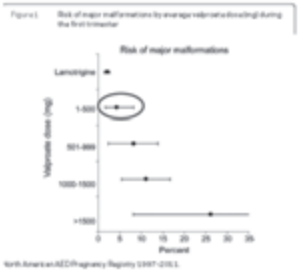
Malformation rate at one year for monotherapy exposure to carbamazepine, phenobarbital, valproic acid and lamotrigine by dose



Tomson and Battino Lancet Neurol 2012

Is the risk dose-dependent?

Data from the North American Registry



Hernandez-Diaz Neurology 2012;78:1692-99

Valproate dose and risk of MCM
The UK Pregnancy Register

E. Mawhinney et al./Seizure 21 (2012) 215–218

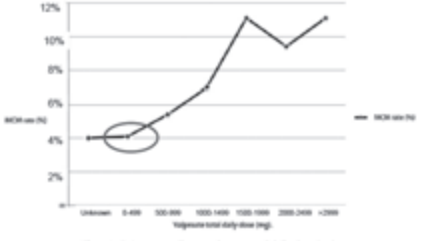
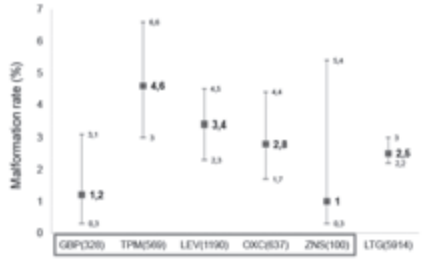


Fig. 1. MCM rate according to valproate total daily dose (mg).

Newer generation AEDs & Malformations

Combined data from 22 reports with different definitions and methods



Data from Tomson & Battino Lancet Neurol 2012, updated May 2013

The NEW ENGLAND JOURNAL of MEDICINE

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Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Kimford J. Meador, M.D., Gus A. Baker, Ph.D., Nancy Browning, Ph.D., Jill Clayton-Smith, M.D., Deborah T. Combs-Cantrell, M.D., Morris Cohen, Ed.D., Laura A. Kalayjian, M.D., Andres Kanner, M.D., Joyce D. Liporace, M.D., Page B. Pennell, M.D., Michael Privitera, M.D., and David W. Loring, Ph.D., for the NEAD Study Group*

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

Summary

Cognitive function at 3 years

Median Dose
CBZ 800 mg
LTG 500 mg
PHT 400 mg
VPA 1000 mg

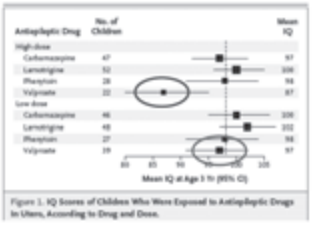


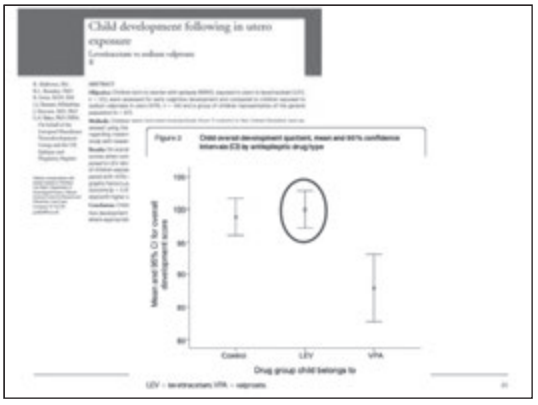
Figure 1. IQ Scores of Children Who Were Exposed to Antiepileptic Drugs in Utero, According to Drug and Dose.

Cognitive function at 6 years

	N	Mean age-6 IQ (95% CI)	p value (vs below-median dose valproate)	p value (vs above-median dose valproate)
Carbamazepine (median dose 700 mg per day)				
Below group median	28	107 (102-112)	0·2994	0·0002
Above group median	33	106 (102-110)	0·5990	0·0004
Lamotrigine (median dose 433 mg per day)				
Below group median	31	106 (102-111)	0·4854	0·0003
Above group median	43	109 (105-113)	0·1154	<0·0001
Phenytoin (median dose 258 mg per day)				
Below group median	20	108 (103-114)	0·2553	0·0002
Above group median	20	106 (101-112)	0·5501	0·0011
Valproate (median dose 1000 mg per day)				
Below group median	21	104 (99-109)	NA	0·0065
Above group median	26	94 (90-99)	0·0065	NA

Means were adjusted for maternal IQ, gestational age at birth, and folate. IQ=intelligence quotient.

Table 5: IQ outcomes at age 6 years by median group dose for the age-6-completer sample (n=224)



Child development following in utero exposure

Lamotrigine vs sodium valproate

Figure 2: Child overall development quotient, mean and 95% confidence intervals (CI) by antiepileptic drug type

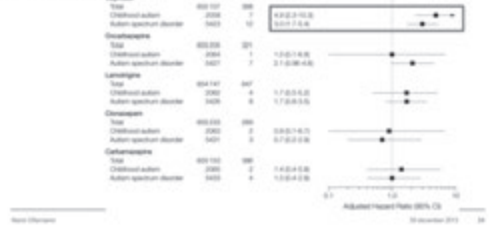
LEV = levetiracetam; VPA = valproate.

Behavioural outcomes after exposure to AEDs

JAMA 2013;309:1696

Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism

Absolute risk of autism spectrum disorder 4.4% (2.6-7.5%) after VPA exposure



JNNP January 2013

The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs

ASD, ADHD, Dyspraxia

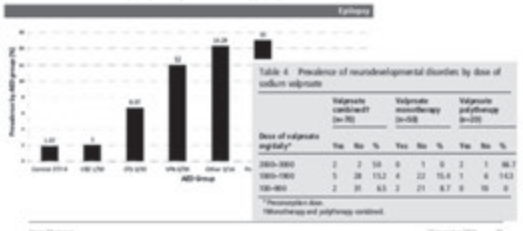


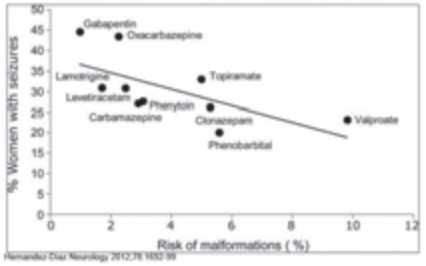
Table 4 Prevalence of neurodevelopmental disorders by dose of sodium valproate

Dose of valproate mg/day*	Valproate combined† (n=76)			Valproate monotherapy (n=58)			Valproate polytherapy (n=20)		
	Yes	No	%	Yes	No	%	Yes	No	%
1001–2000	2	2	50	0	1	0	2	1	66.7
1000–1000	5	28	15.2	4	22	15.4	1	4	14.3
100–800	2	31	6.5	3	21	8.7	0	10	0

*Phenobarbitone dose.
†Monotherapy and polytherapy combined.

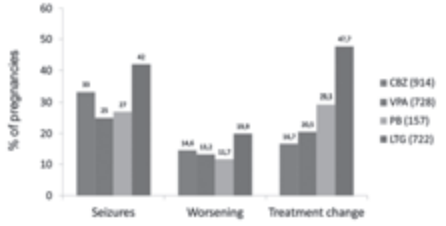
Teratogenic potential has to be weighed against efficacy

Seizure Control and Risk of Malformations NAAPR



Hernandez Diaz Neurology 2012;78 1692-99

Seizure control and treatment changes during pregnancy



Effects of pregnancy on pharmacokinetics of AEDs

Tomson et al., Epilepsia 2013

Differential Effects of Pregnancy on PK of different AEDs

AED	Total conc.	Unbound conc.
Phenobarbital	-10-20%	-10-20%
Phenytoin	-60%	-20%
Carbamazepine	-10%	minor
Valproate	-30%	minor
Lamotrigine	-30-75%	-30-75%
Levetiracetam	-40-50%	Probably -40-50%
Oxcarbazepine	-30-50%	Probably -30-50%
Topiramate	-30-35%	Probably -30-35%

But, differences between patients on same AED!

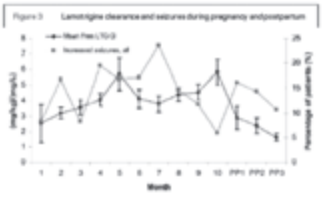
Tomson et al., Epilepsia 2013

Declining AED levels and Seizure Control

The case of lamotrigine

Increased seizure frequency in 39% of 36 pregnancies associated with a lower ratio to target concentration (RTC)

RTC < 0.65 is a predictor of seizure worsening



Pennell *et al.* Neurology 2008;78:2130-6

Folate to reduce fetal risks?

- 0.8 mg folate/day to general population of childbearing age reduce risk of birth defects [1]
- 4 mg/day reduce risk of NTD in high risk group but WWE excluded
- No support for effectiveness of folate in reducing ***AED related birth defects*** in
  - →Swedish Medical Birth registry [3]
  - →North American Pregnancy Registry [4,5]
  - →UK Pregnancy Registry [6]
  - →EURAP [7]
- But folate might improve cognitive outcome
  - →NEADs study[8]

Multivariable logistic analysis

Including 10 co-variates in addition to treatment categories
Data from EURAP, Tomson et al Lancet Neurol 2011

	Odd Ratio (95% CI)	p value
Non-drug covariates		
Americas vs Europe	2.1 (0.82-5.33)	0.1227
South-East Asia vs Europe	1.3 (0.59-2.94)	0.5064
Western Pacific vs Europe	1.0 (0.67-1.63)	0.8570
Parental history of major congenital malformations	4.4 (2.06-9.23)	0.0001
Maternal age	1.0 (0.97-1.04)	0.8209
Educational level father (low vs medium/high)	1.0 (0.64-1.55)	0.9941
Educational level mother (low vs medium/high)	1.1 (0.70-1.73)	0.6829
Generalized tonic-clonic seizures during first trimester	0.6 (0.31-1.11)	0.103
Folic acid use (appropriate vs inappropriate)	1.4 (1.02-1.82)	0.035
Sex (male vs female)	1.0 (0.75-1.29)	0.8982
Idiopathic generalized epilepsy vs localisation-related epilepsy	0.9 (0.62-1.23)	0.4421
Undetermined/unclassifiable vs localisation-related epilepsy	0.8 (0.47-1.22)	0.2531
Parity	0.8 (0.67-1.04)	0.1074

Odd ratios for maternal age and parity show the risk associated with an increase of 1 year in age an d an increase of 1 point in parity, respectively.

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

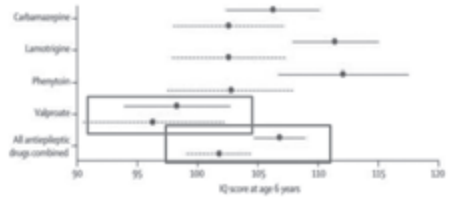


Figure 3 Child IQ at 6 years, by exposure to maternal antiepileptic drug use and periconceptional folate. Mean (95% CIs) are shown for folate (solid lines) and no folate (dashed lines). For carbamazepine, 56 children were exposed to periconceptio...

The Lancet Neurology Volume 12, Issue 3 2013 244 - 252

Exposure after birth
Breast-feeding and AED levels

- Sufficient data for safe breast-feeding
  - phenytoin, carbamazepine, valproate, levetiracetam
- Reasonable data, significant levels, uncertain if AE
  - lamotrigine
- Reasonable data AE could occur
  - Phenobarbital, ethosuximide
- Limited data, no signals of AE
  - Gabapentin, topiramate
- Insufficient data
  - Oxcarbazepine, zonisamide, pregabalin, lacosamide, eslicarbazepinacetate

No difference in IQ at 3 years between breast-fed and not breast-fed infants of mothers taking valproate, lamotrigine, carbamazepine, or phenytoin
Meador et al Neurology 2010

Could breast-feeding affect cognitive development?

Table 3 Adjusted mean age 3 IQ by antiepileptic drug (AED) group

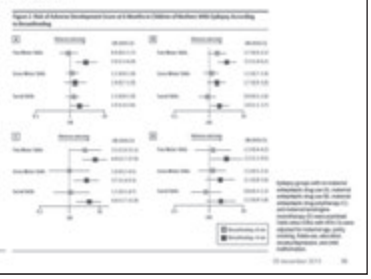
AED group	Breastfed	No.	Age 3 IQ*	95% Confidence Interval*
All AEDs	Yes	84	99	96-103
	No	115	98	95-101
Carbamazepine	Yes	26	103	97-108
	No	32	98	93-103
Lamotrigine	Yes	30	104	97-110
	No	36	104	98-110
Phenytoin	Yes	17	91	84-98
	No	23	99	93-105
Valproate	Yes	11	93	82-105
	No	24	90	83-98

* Mean age 3 years IQs adjusted for maternal IQ, maternal age, dose, gestational age, and folate. Means were also adjusted for AED group in the "all AEDs" category.
† None of the breastfed vs nonbreastfed comparisons was significant.

Meador et al., Neurology 2010

Breast-feeding and Development

Early Child Development and Exposure to Antiepileptic Drugs Prenatally and Through Breastfeeding
A Prospective Cohort Study on Children of Women With Epilepsy



How can risks be minimized?

Re-evaluate AED treatment before pregnancy

- → Consider withdrawal in women in remission
  - If the recurrence risk is low and woman willing to take the risks
  - If sufficient time available for assessment before pregnancy
- → Consider conversion from poly- to monotherapy
  - If risk of deterioration is low
- → Select the most appropriate AED with respect to teratogenicity as well as seizure control
  - If possible avoid valproate in particular at doses >500 mg/day
- → Establish lowest effective dose
- → Establish optimal pre-pregnancy AED levels
- → Prescibe folate, but explain lack of solid evidence
- → Offer prenatal diagnosis
- → Monitor AED levels where available
  - In particular lamotrigine, but also oxcarbazepine and levetiracetam

General conclusions

- Encourage planned pregnancies and optimise treatment before conception
- Urgent need for alternatives to valproate
- Monitor treatment more closely during pregnancy
  - → Avoid major changes (switch) during pregnancy
- Encourage breast-feeding
- Come to Stockholm next summer, learn more and continue the discussion….!

The 11th European Congress on Epileptology will take place in Stockholm, Sweden, from 29th June - 3rd July 2014.

The European Congress on Epileptology (ECE) is now a landmark in the epilepsy community agenda and the Stockholm 2014 congress will build on the success of the 10th ECE in London. The programme will cover cutting-edge research in the field of epilepsy through presentations from the leaders in the field, including lectures by world-renowned scientists on topics at the interfaces of epilepsy.

We look forward to welcoming you to Stockholm,

Kristina Malmgren IOC Co-chair | **Meir Bialer** IOC Co-chair | **Torbjörn Tomson** SAC Chair

11th European Congress on Epileptology
STOCKHOLM
29th June - 3rd July 2014

www.epilepsystockholm2014.org

Sergiusz Jozwiak (Poland)

TUBEROUS SCLEROSIS

Rodrigo Cunha (Portugal)

ASTROCYTE-NEURON HOMEOSTASIS

Helen Scharfman (USA)

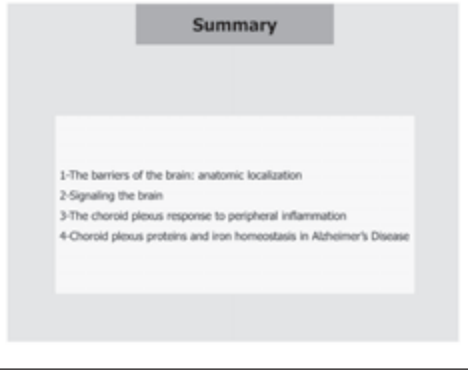
NEUROGENESIS IN EPILEPSY

Sergiusz Jozwiak (Poland)

WEST SYNDROME

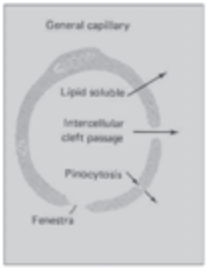
Joana Palha (Portugal)

BLOOD-BRAIN BARRIERS II



How do molecules and cells circulating in the blood reach most of the organs?

Most capillaries of the body are fenestrated

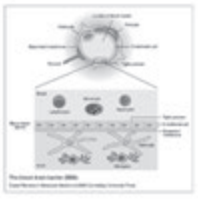


What about the brain??

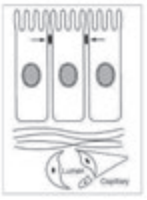
The barriers of the brain

The blood-brain barriers

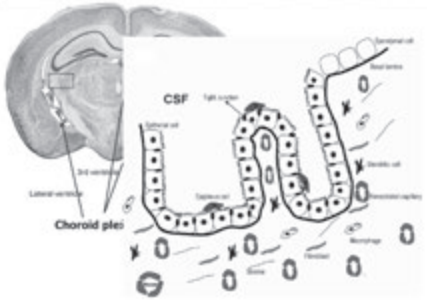
Blood-brain barrier (BBB)



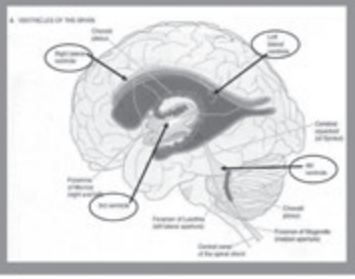
Blood-cerebrospinal fluid barrier (BCSFB)



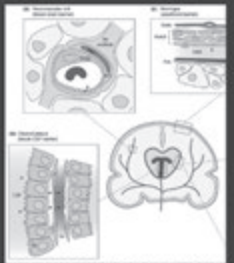
Where is the choroid plexus?



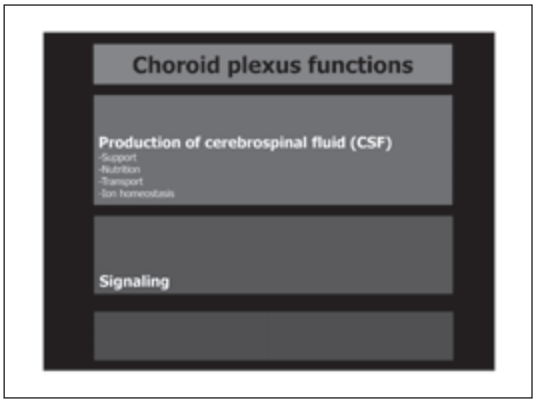
Brain ventricles

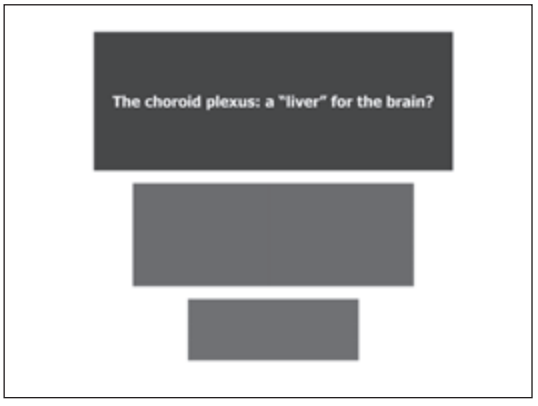


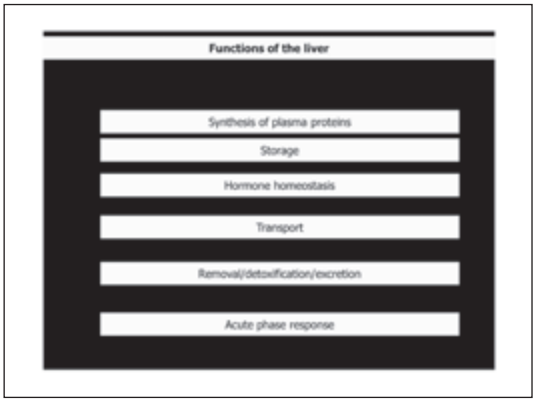
Barriers: summary



Saunders NR et al, 2008. Trends Neurosci 31:279-286


Choroid plexus functions
Production of cerebrospinal fluid (CSF)
-Support
-Nutrition
-Transport
-Ion homeostasis
Signaling


The choroid plexus: a "liver" for the brain?


Functions of the liver
Synthesis of plasma proteins
Storage
Hormone homeostasis
Transport
Removal/detoxification/excretion
Acute phase response


Signaling:
Acute phase response

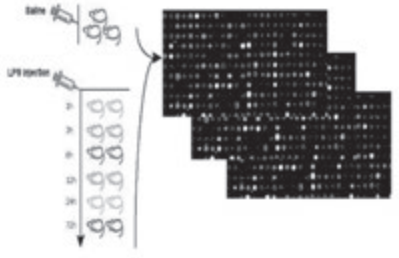
How does the choroid plexus respond to peripheral inflammation?

Marques *et al.* 2009 J Cereb Blood Flow Metab 29:921-32
Marques *et al.* 2009 BMC Neurosci 10:135
Marques *et al.* 2009 Endocrinology 150:2822-8
Marques *et al.* 2011 Fluids Barriers CNS 8:10

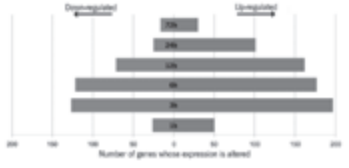
"*Interesting*" choroid plexus proteins

-LPS receptor: TLR-4
-Prostaglandin biosynthesis: COX-1 and COX-2
-**Adhesion molecules**: ICAM, VCAM-1
-**Interleukins**: IL-1, IL-6, IL-10, TNF
-**Tissue remodeling factors**: TIMP2, TIMP3

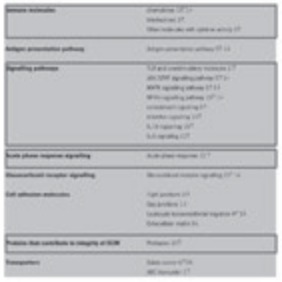
Experimental planning



Nº of genes with altered expression



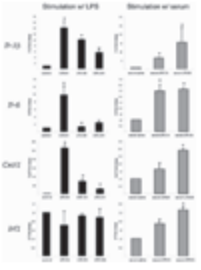
The choroid plexus displays an acute phase response



Which cells are mediating this response?

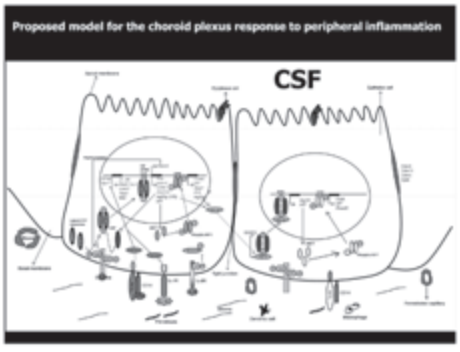
Primary cultures of choroid plexus cells establish an efficient barrier

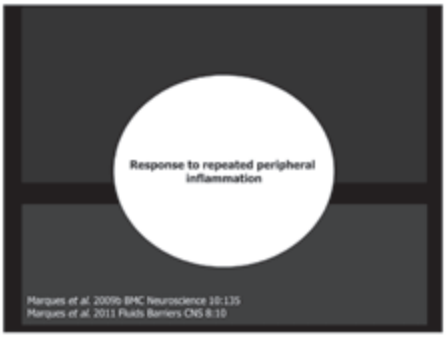
In vitro stimulation of cultures of rat choroid plexus primary cells



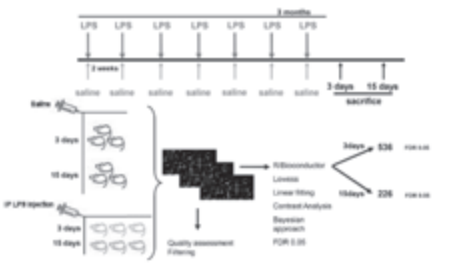
LPS alone but also other molecules whose concentration increases in the blood in response to LPS trigger the choroid plexus response.

Proposed model for the choroid plexus response to peripheral inflammation



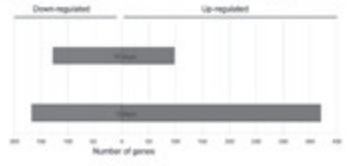


The CP response to a sustained peripheral inflammatory stimulus

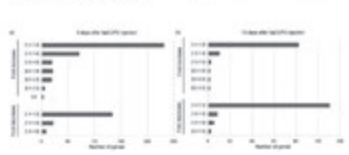


The CP response to a repeated peripheral inflammatory stimulus

Number of genes whose expression is found altered after a repeated peripheral injection of LPS

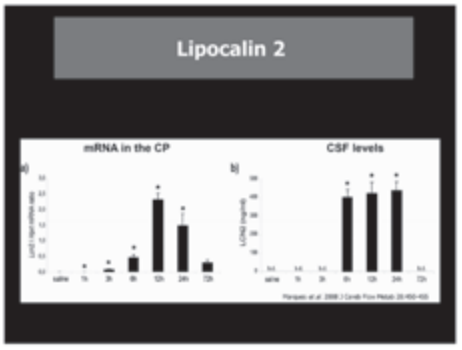


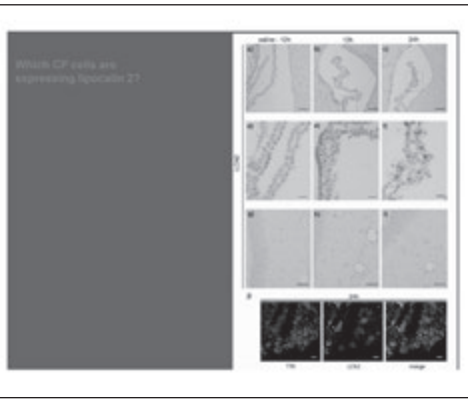
The CP response to a repeated peripheral inflammatory stimulus

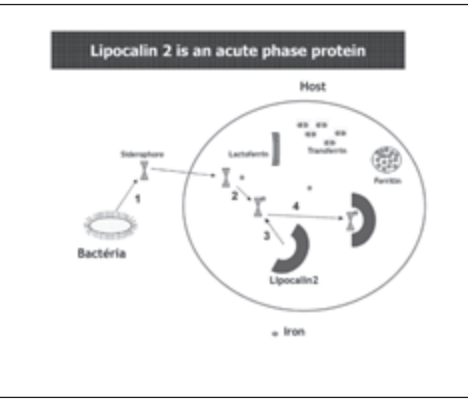


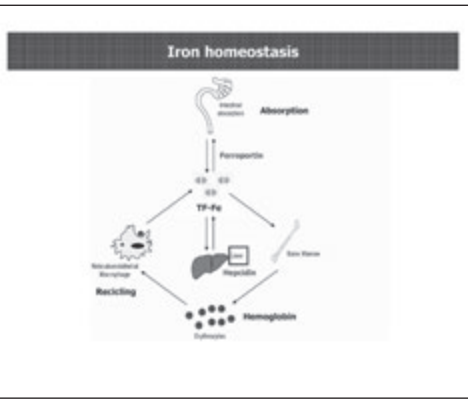
The CP fold change in most genes is below 50% both at 3 and 15 days after the last LPS injection

The choroid plexus response to LPS is varied

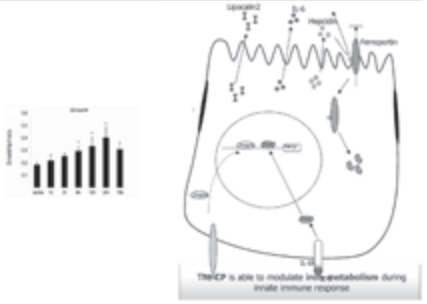

Lipocalin 2
mRNA in the CP
CSF levels




Lipocalin 2 is an acute phase protein
Host
Siderophore
Lactoferrin
Transferrin
Ferritin
Bactéria
Lipocalin2
Iron


Iron homeostasis
Absorption
Ferroportin
TF-Fe
Hepcidin
Recicling
Hemoglobin

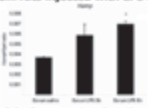
CP iron metabolism in response to peripheral inflammation



TNFCP is able to modulate iron metabolism during innate immune response

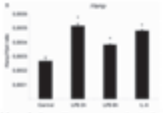
The **epithelial cells** response *in vitro* is similar to that observed *in vivo*

1. Stimulation wih serum from rats injected with LPS or saline solution



The epithelial cells response is similar to that observed *in vivo*

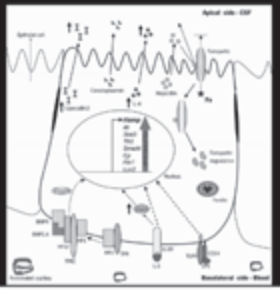
2. Stimulation with LPS or IL-6 alone



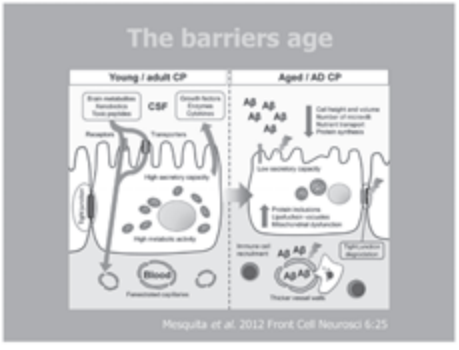
IL-6 alone is able to induce *Hamp* gene *in vitro* in the epithelial cells

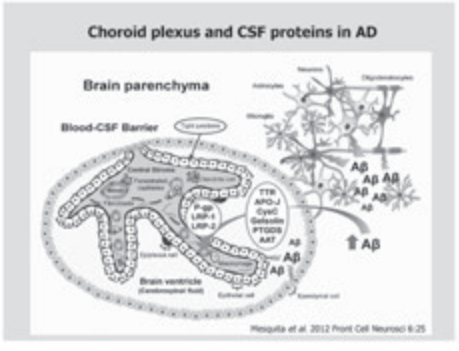
* *P* < 0.05

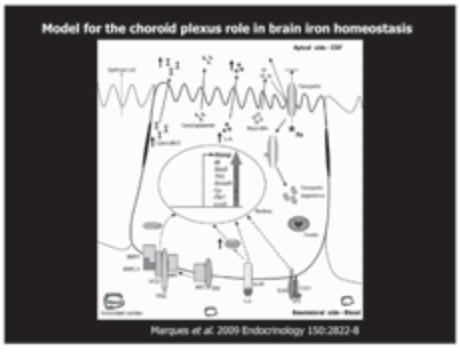
Model for the choroid plexus role in brain iron homeostasis



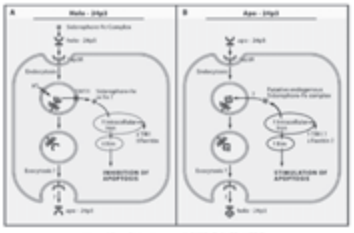

In aging and in AD
Iron homeostasis
Sousa et al. 2007 Neurobiol Learn Mem 88:381–385
Sousa et al. 2007 Neurobiol Aging 28:713-8
Marques et al. 2008 J Cereb Flow Metab 28:450-455
Marques et al. 2009 Endocrinology 150:2822-8
Mesquita et al. 2012 Front Cell Neurosci 6:25
Oliveira et al. 2013 Front Cell Neurosci 7:122
Mesquita et al. 2013 under review


The barriers age
Young / adult CP
Aged / AD CP
CSF
Blood
Mesquita et al. 2012 Front Cell Neurosci 6:25


Choroid plexus and CSF proteins in AD
Brain parenchyma
Blood-CSF Barrier
Aβ
Brain ventricle
Mesquita et al. 2012 Front Cell Neurosci 6:25

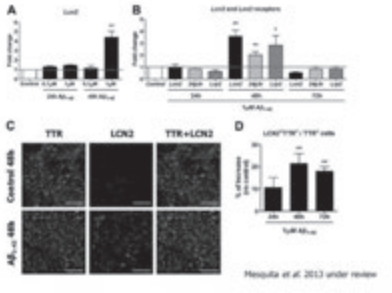

Model for the choroid plexus role in brain iron homeostasis
Marques et al. 2009 Endocrinology 150:2822-8

LCN2 is involved in iron uptake and release from cells



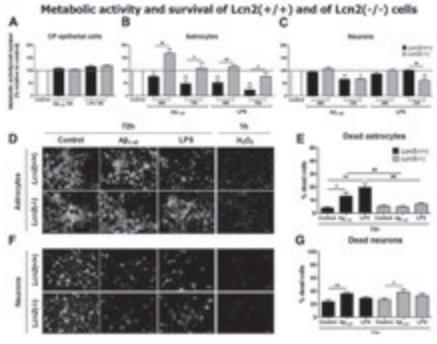
Adapted from Richardson, *et al.*, 2009, Cell 123:1175-7

CP epithelial cells express *Lcn2* in response to Aβ1-42

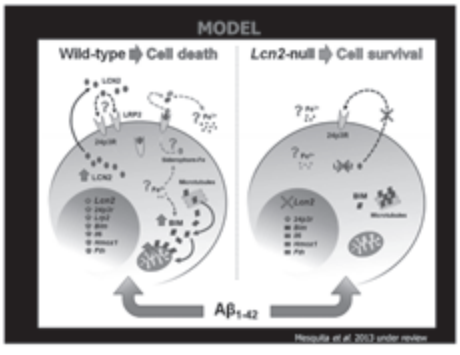


Mesquita *et al.* 2013 under review

Metabolic activity and survival of Lcn2(+/+) and of Lcn2(-/-) cells

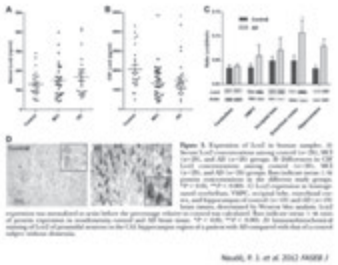


MODEL



Mesquita *et al.* 2013 under review

LIPOCALIN 2 IN HUMAN AD



Naudé, P. J. *et al.* 2012 FASEB J

Slide 44

PT

Interessante que a lipocalina se repete na clínica e no SNC.

Eh curioso com AD.

Homochromatosis gene accelerates the onset of AD by five years, has validated the interest of iron in AD. Also, the presence of an iron-responsive element in APP. In the biochemical level, iron, zinc and copper have been shown to accelerate the aggregation of Ab peptide and enhance metal catalized oxidative stress associated with amyloid plaque formation. All these have encouraged the development of iron chelators as a major new therapeutic strategy for the treatment of AD, running parallel with the development of a vaccine.

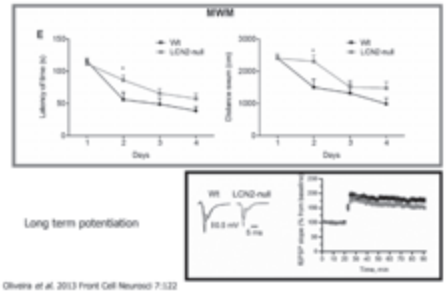
Iron is involved in inflammation, and this may link the inflammatory component of AD and of other chronic disorders.

There is a direct link between iron and AD, demonstrated by the presence of an iron-responsive element in the 5'-UTR of the APP transcript.

Dysregulation of brain iron homeostasis is central in early neuropathological events in AD, including oxidative stress, inflammatory processes, amyloid deposition, tau phosphorylation, and neuronal cell cycle regulatory failure, leading to apoptosis (states that cell cycle arrest could prevent neuronal apoptosis. Stores their iron chelators, real only halt cell cycle but also promote synaptogenesis which may be an indication of rescuing neurons). There is a direct link between iron and AD, demonstrated by the presence of an iron-responsive element in the 5'-UTR of the APP transcript. As a consequence to these findings, a new paradigm is emerging that recruits the development of iron-chelating neuroprotective neuroscience drugs with multimodal functions, acting at various pathological brain targets.

Apenas clínico e sobre precipitam Ab. O ferro encontra-se na vizinhança de placas de AD mas precipitamento concomitante com ferritina nos processos neuríticos associados às placas.

LCN2(-/-) mice display cognitive impairment

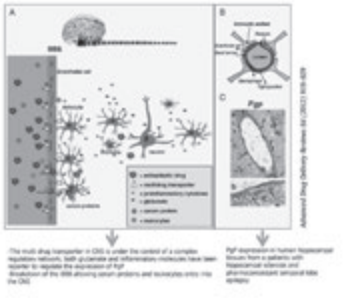


Long term potentiation

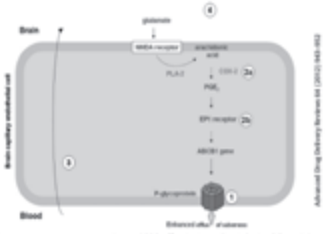
Oliveira *et al.* 2013 Front Cell Neurosci 7:122

In the context of epilepsy

Representation of the cellular expression of drug transporters in the epileptic brain

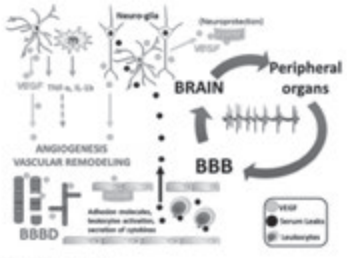


Role of CNS efflux drug transporters in antiepileptic drug delivery: overcoming CNS efflux drug transport



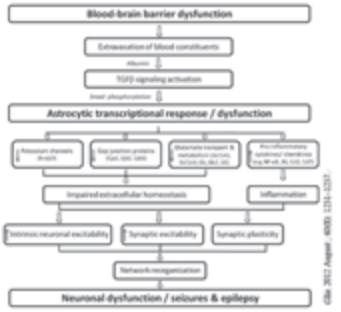
Different options to target or overcome enhanced BBB efflux in the epileptic brain: (1) modulation of Pgp transport function, (2a and b) blocking the signaling pathway that up-regulated Pgp in response to seizure activity, and by-passing BBB transporters by encapsulation of the antiepileptic drugs (3) or intracerebral administration (4).

The role of the blood-brain barrier (BBB) in epilepsy has evolved from an obstacle for drug brain delivery to an etiological factor contributing to seizures.

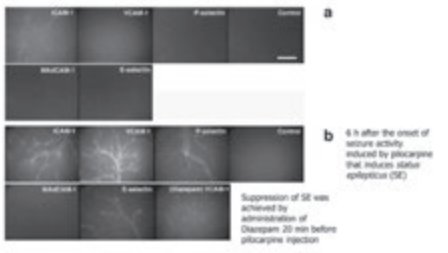


Neurocomistry 2013 June ; 19(3): 304–312.

BBB dysfunction and astrocytic dysfunction in epilepsy

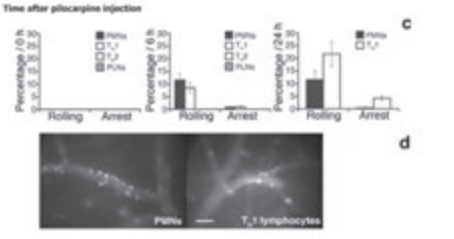


Expression of adhesion molecules in cortical vessels in baseline (a) and 6 h after the onset of seizure activity



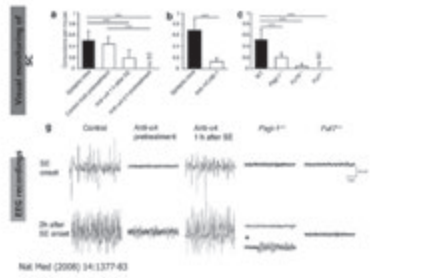
Nat Med (2008) 14:1377-83

Immune cells in the brain barriers in the epileptic brain



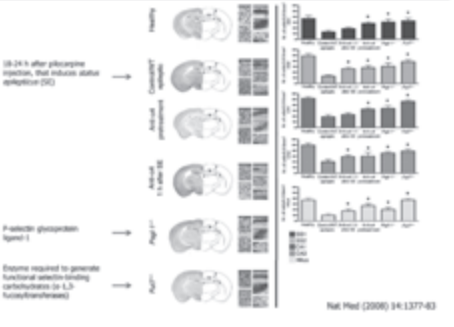
Nat Med (2008) 14:1377-83

Effect of blockade or deficiency in leukocyte adhesion mechanisms on convulsions and seizures

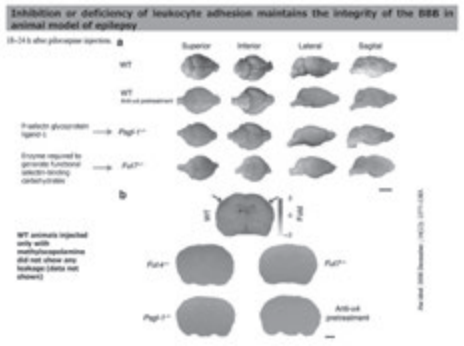


Nat Med (2008) 14:1377-83

Effect of blockade or deficiency in leukocyte adhesion on neuronal cell



Nat Med (2008) 14:1377-83

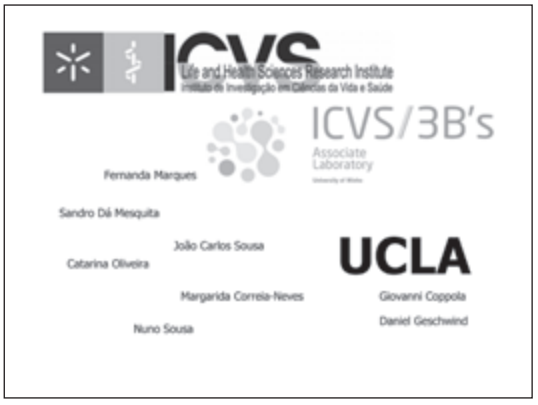


What about the choroid plexus?

Therefore

The barriers are more than mere obstacles, they are part of the game

Neuroscience Research Domain


ICVS
Life and Health Sciences Research Institute
ICVS/3B's
Associate Laboratory
Fernanda Marques
Sandro Dá Mesquita
João Carlos Sousa
Catarina Oliveira
Margarida Correia-Neves
Nuno Sousa
UCLA
Giovanni Coppola
Daniel Geschwind

Rodrigo Cunha (Portugal)

CAFFEINE AND ADENOSINE RECEPTORS IN THE CONTROL OF EPILEPTIC-LIKE FEATURES

Torbjorn Tomson (Sweden)

ANTIEPILEPTIC DRUGS AND SUDEP

Sudden Unexpected Death in Epilepsy SUDEP and Antiepileptic Drugs

LASSE February, 2014

Torbjörn Tomson
Department of Clinical Neuroscience
Karolinska Institutet
Stockholm, Sweden

SUDEP Definitions & Awareness

On 19 March 2011, Knut collapsed and died in his enclosure. Witnesses reported that after the bear's rear **left leg began shaking**, he became agitated before **convulsing** several times and **falling backwards into the pool**. Approximately 600 to 700 zoo visitors witnessed Knut's death. On 1 April, pathology experts announced that the bear's apparent seizure was due to his suffering from **encephalitis**. This suspected infection must already have been there for a long time ... at least several weeks, possibly months". It was also announced that **had Knut not drowned after collapsing, he would not have survived**. Knut's sudden death caused an international outpouring of grief. The Zoo plans to erect a monument in Knut's honor, financed by donations from fans.

Wikipedia 2012.04.20

Defining SUDEP

- Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause of death

Nashef Epilepsia1997;38

CRITICAL REVIEW AND INVITED COMMENTARY

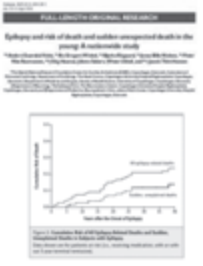
Unifying the definitions of sudden unexpected death in epilepsy

*Lina Nashef, †Ilkon L. So, ‡Philippe Ryvlin, and §Torbjörn Tomson

- Unified definition and classification proposed
  Nashef , So, Ryvlin, Tomson Epilepsia 2012;53:227
  - Distinction between cases with competing cause (Possible SUDEP) and cases with insufficient information (Unclassified)
  - Distinction between combined causes (SUDEP plus) and competing non-SUDEP related cause of death (Possible SUDEP)
  - Separate category for cases surviving resuscitation (Near-SUDEP)
  - Criteria for "Sudden" specified (<1hour)

SUDEP is an issue!

- The risk of Sudden Unexpected Death among young people with epilepsy16- to 24-fold higher than in the general population increase in risk of sudden death
  Holst A Epilepsia 2013, Ficker DM. Neurology 1998;51:1270
- SUDEP accounted for 30% of all deaths in long-term follow-up people diagnosed with epilepsy in childhood. Cumulative risk of SUDEP at 40 years 7%
  Sillanpää and Shinnar NEJM 2010



Incidence of SUDEP varies with the epilepsy population

Karolinska Institutet

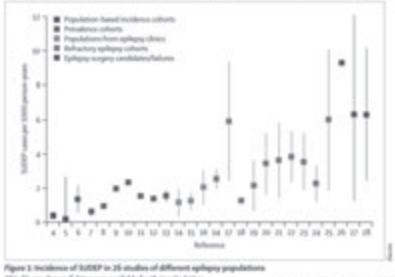


Figure 1: Incidence of SUDEP in 25 studies of different epilepsy populations
95% CIs are shown if data were available for their calculation.

Tomson et al Lancet Neurol 2008

FULL-LENGTH ORIGINAL RESEARCH

Combined analysis of risk factors for SUDEP

*Dale C. Hesdorffer, †Torbjörn Tomson, ‡Emma Benn, §Joseph W. Sander, ¶Lena Nilsson, [Yvonne Langan, **Thaddeus S. Walczak, ††Ettore Beghi, ‡‡Martin J. Brodie, and *Allen Hauser, for the ILAE Commission on Epidemiology; Subcommission on Mortality

Study	Number cases and controls	Matching factors	Inclusion criteria
US (Walczak et al, 2001)	20 cases 80 controls	Month and study center	
Sweden (Nilsson et al, 1999)	56 cases 157 controls	Birth year, sex, and assessment period	15-70 years ≥1 year of VPA, PHT, or CBZ
Scotland (Hitiris et al, 2007)	64 cases 119 controls	Birth year, gender and syndrome classification	Active seizure disorders
England (Langan et al, 2005)	149 cases 602 controls	Age and geographic location	16 to 50 years

Generalised tonic-clonic (GTC) seizures major risk factor

GTC frequency per year	Adjusted* OR (95% CI)
0	1.0 (Referent)
1-2	5.1 (2.9-8.8)
>=3	15.5 (9.9-24.1)
Unknown	5.4 (3.2-8.9)
No GTCS	1.0 (Referent)
>=1 GTCS/year or Unknown # GTCS/year	7.1 (4.5-11.0)

*Adjusted for data source, gender, age at death and duration of epilepsy

Hesdorffer et al Epilepsia 2011;52:1150

Adjusted Odds Ratios

For data source, gender, age at death and duration of epilepsy

Variable	Adjusted OR (95% CI)
Gender	
Female	**1.0 (Referent)**
Male	**1.42 (1.07-1.88)**
Onset age	
<16 years	**1.72 (1.23-2.40)**
16-60 years	**1.0 (Referent)**
>60 years	**0.41 (0.08-2.14)**
Duration of epilepsy	
<15 years	**1.0 (Referent)**
>15 years	**1.95 (1.45-2.63)**
Idiopathic Etiology	
No	**1.0 (Referent)**
Yes	**0.71 (0.50-1.01)**

Hesdorffer et al Epilepsia 2011

FULL-LENGTH ORIGINAL RESEARCH

Combined analysis of risk factors for SUDEP

Table 1. Continued

*Adjusted for data source, gender, age at death and duration of epilepsy

Can specific AEDs increase SUDEP risk?

FULL-LENGTH ORIGINAL RESEARCH

Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: A nested, case-control study

16 definite, 3 probable SUDEPs
Controls: living epilepsy patients

Population	Cases Exposed/All	Controls Exposed/All	Odds Ratio (95% CI)
Patients on LTG	8/19	15/63	2.6 (0.8-8.4)
Women on LTG	7/12	10/41	5.6 (1.1-28.2)

- Possible association between LTG and SUDEP could hypothetically be due to
  - → Direct pharmacological effects of LTG
  - → Poorer control of GTCS in women on LTG
- Control of GTCS not known and not adjusted for

FULL-LENGTH ORIGINAL RESEARCH

Do antiepileptic drugs or generalized tonic–clonic seizure frequency increase SUDEP risk? A combined analysis

Dale C. Hesdorffer, Torbjörn Tomson, Emma Benn, Josemir W. Sander, Lena Nilsson, Yvonne Langan, Thaddeus S. Walczak, Ettore Beghi, Martin J. Brodie, and W. Allen Hauser for the ILAE Commission on Epidemiology (Subcommission on Mortality)

Analysis of lamotrigine, data from England and USA

Treatment	Crude analysis Odds ratio (95% CI)	Adjusted analysis* Odds ratio (95% CI)
No AED	1.00 (reference)	1.00 (reference)
Other AED	1.1 (0.6-1.9)	0.7 (0.4-1.4)
LTG monotherapy	1.5 (0.4-6.2)	0.7 (0.1-3.6)
LTG polytherapy	2.9 (1.4-6.0)	0.95 (0.4-2.2)

*Adjustment for GTCS frequency

FULL-LENGTH ORIGINAL RESEARCH

Sudden unexpected death in epilepsy in lamotrigine randomized-controlled trials

Torbjörn Tomson, Lawrence J. Hirsch, Daniel Friedman, Nicolette Bester, Anne Hammer, Michael Irizarry, Lianna Ishihara, Alok Krishen, Theodore Spalding, Art Wamil, and Robert Leadbetter

7,774 subjects in 42 RCTs, 8 definite or probable SUDEPs (4 in LTG arm)

Definite/probable SUDEP on LTG treatment vs. Comparator

- OR 0.22 (95% CI 0.00-3.14) in placebo-controlled parallel-group trials
- OR 2.18 (95% CI 0.17-117) in active-comparator parallel-group trials
- OR 1.08 (95% CI 0.00-42.2) in placebo-controlled cross-over trials

Adjunctive treatment (polytherapy) and SUDEP Evidence from Placebo-Controlled RCTs

Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials

Lancet Neurol 2011;10:962.

18 Definite or Probable SUDEPs

SUDEP rate per 1000 patient years
6.9 (3.8-11.6) in Placebo arm
3.7 (0.1-20.6) Non-efficacious dose
0.9 (0.2-2.7) in Efficacious arm

Cause of Death	Efficacious AED vs. Placebo Odds Ratio (95% CI)	P-value
Definite & Probable SUDEP	0.17 (0.05-0.57	0.0046
Other causes of death	0.89 (0.28-2.79)	0.8407

Risk factors in case-control studies

Combined analysis
Hesdorffer et al Epilepsia 2011

- GTCS frequency
- Young age at onset
- Long duration
- Male gender
- Symptomatic etiology

Other sources

- Lack of supervision at night
  → 10-fold increased risk vs. special precautions
  Langan et al Neurology 2005
- Nocturnal seizures
  → OR 2.6 (1.3-5.0)
  Lamberts et al Epilepsia 2012

Conclusions from clinical observations and epidemiological studies

- SUDEP most common epilepsy related cause of death
- Most cases unwitnessed and circumstances unclear
- Often at night and found dead in bed
- When witnessed, in most cases in the after-math of a generalized tonic-clonic seizure
  - → Mechanisms likely to be multiple
- Most people with epilepsy don't die from SUDEP
  - → Individual susceptibility
- Most who die have had numerous non-fatal seizures
  - → Unknown triggering factors make a seizure fatal

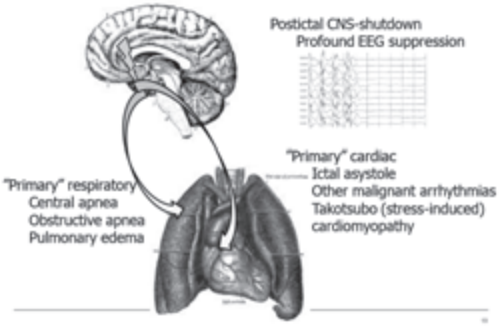
Some suggested predisposing factors

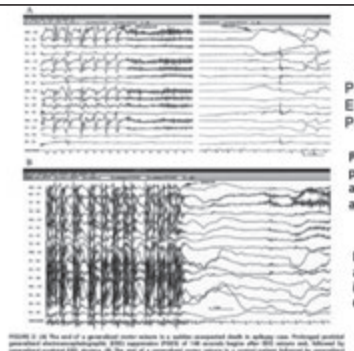
- Channelopathies related to Long QT-syndome
  - → Co-occurrence of epilepsy in mouse model with LQT mutation
  - → KCNQ knock-out mice may be SUDEP model
  - → Family with SCN1A mutation and SUDEPs
  - → Mutations in SCN5A or KCNH2 genes in 6/68 SUDEP cases
- Impairment of autonomic cardiac control
  - → Heart rate variability (HRV) decreased in chronic epilepsy
  - → Diurnal variation in HRV decreased
  - → Seizures may affect HRV
  - → HRV not different between cases and controls (n=7/7)
- Prolonged postictal EEG-flattening
  - → Clinical study suggests that postictal EEG flattening is prolonged in patients at risk of SUDEP

Predisposing factors and triggers

Figure 2: Interaction between proposed predisposing factors and triggers for SUDEP

SUDEP Mechanisms





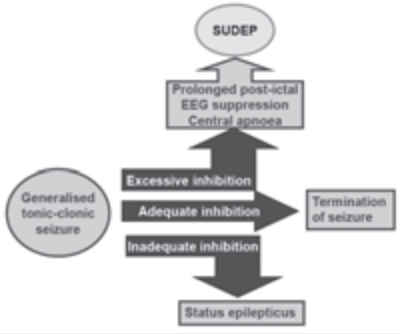
10 SUDEPs
30 Controls

Prolonged Postictal EEG Suppression as Predictor of SUDEP

PGES= immediate postictal generalized absence of EEG activity >10μV

PGES of >50 sec associated with increased risk OR 5.2

Lhatoo et al Annals Neurol 2010

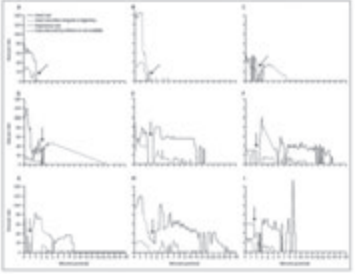


Modified after Lhatoo 2011

Clues from monitored SUDEP

- 147 EMUs surveyed
- 16 SUDEP and 9 near-SUDEP identified (2 dealyed fatalities)
- 11/18 SUDEP occurred during active monitoring (5 previously published)
  - → All fatalities adults
  - → All SUDEP and fatal near-SUDEP during evening or night
  - → Preceded by a GTCS in all fatalities
  - → Cardiorespiratory resuscitation with a delay of >10 minutes after apnoea in all fatalities
  - → Postictal cardiorespiratory dysfunction in all:

Patterns of postictal cardiorespiratory functions in 9 SUDEP cases



Posticalt sequence

Generalized tonic-clonic seizure

- Short period of normal or increased heart and respiratory rates
- Combination of central apnea, severe bradycardia
- Transient asystole together with generalised EEG suppression

- In a proportion of cases transient restoration of cardiac function together with abnormal ineffective respirationprogressively deteriorating until terminal apnea, preceding terminal asystole

How can SUDEP be prevented?

Figure 2: Interaction between proposed predisposing factors and triggers for SUDEP

Tomson et al Lancet Neurol 2008

Improving seizure control

- By use of anitepileptic drugs
  - Treatment rather than no treatment
  - Add-on in refractory patents
  - Enhance compliance
- By use of epilepsy surgery
- With information

AEDs and SUDEP Risk

Extended analysis

Adjusting for data source, gender, age at death and GTCS frequency

Variable	Adjusted OR (95% CI)
No AED therapy	1.0 (Referent)
1 AED	0.5 (0.3-0.995)
2 AEDs	0.9 (0.4-1.8)
3 AEDs	2.0 (0.9-4.1)
>3 AEDs	1.6 (0.6-4.1)

Monotherapy with AEDs appears to be protective
No significant increase in risk with polytherapy when adjustment is made for seizure frequency

Hesdorffer et al Epilepsia 2012

Compliance with AED therapy and mortality

Nonadherence to antiepileptic drugs and increased mortality

Findings from the RANSOM Study

Neurology. 2008 Nov 11;71(20):1572-6.

Nonadherence vs Adherence to prescribed AEDs
Hazard Ratio (95%CI) 3.32 (3.11-3.54)

28

Compliance with AED therapy and mortality

Research Br J General Practice May 2011

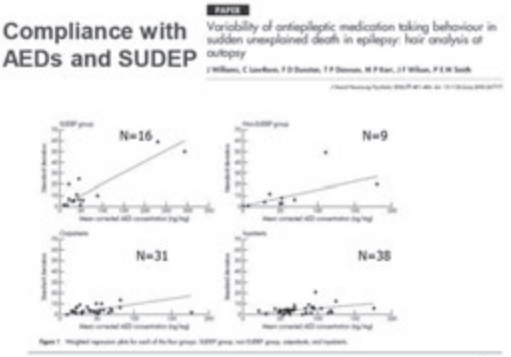
Epilepsy mortality and risk factors for death in epilepsy:

a population-based study

Time since last AED prescription	Controls	Cases	Odds ratio Death (95% CI)
<90 days	10 847	8250	Reference
91-182 days	768	1117	1.83 (1.66-2.03)

29

Compliance with AEDs and SUDEP



PAPER

Variability of antiepileptic medication taking behaviour in sudden unexplained death in epilepsy: hair analysis of autopsy

N=16

N=9

N=31

N=38

30

Epilepsy surgery and SUDEP

Incidence of SUDEP (per 1,000 person years) in different epilepsy surgery case series

Source		Association with seizure control after surgery
Salanova US	215 TLE	Unclear
Sperling US	583	Incidence 0.0 among seizure free 6.3 if recurrent seizures
Nilsson SWE	596	0/6 SUDEP among seizure free
Bell UK	561	0/5 SUDEP among seizure free
Seymour UK	306 TLE	2/6 SUDEP among seizure free (?) patients

Salanova et al., Epilepsia 2002;43:170, Sperling Epilepsia 2005;46(Suppl.11):49
Seymour 2012 Epilepsia 2012;53:262, Nilsson Epilepsia 2003;44:575, Bell et al., JNNP 2010;81:716-8

Epilepsy surgery and SUDEP
Seizure control and SUDEP risk

Source	Surgery cases, n	SUDEP N	Incidence Seizure free	Incidence Seizures
Salanova US	215 TLE	3(6?)	2.0 (4.0?)	
Sperling US	583	10	0	6.3
Nilsson SWE	596	6	2.4	6.3
Bell UK	561	5	1.3	4.5
Seymour UK	306 TLE	6	1.7	

Salanova et al., Epilepsia 2002;43:170, Sperling Epilepsia 2005;46(Suppl.11):49
Seymour 2012 Epilepsia 2012;53:262, Nilsson Epilepsia 2003;44:537), Bell et al., JNNP 2010;81:716-8

Epilepsy surgery and SUDEP

- SUDEP incidence after surgery
  - → In the same range as for the general epilepsy population
  - → Lower than among cases evaluated for and denied surgery
  - → Lower than rates reported for surgery candidates
  - → Lower among seizure free than among patients with seizure recurrence after surgery
- Evidence for protective effect of surgery?
  - → Possibility of biological differences (of relevance for SUDEP risk) between suitable vs. unsuitable surgery candidates, and good vs. poor responders to surgery cannot be excluded
  - → Circumstantial

Adequate supervision of high risk patient may reduce risk

	Cases (n)	Controls (n)	OR 95%CI
No supervision	**109**	**169**	**1**
Same room	**34**	**156**	**0.4 (0.2-0.8)**
Special precautions*	**11**	**42**	**0.1 (0.0-0.3)**

*regular checks throughout night or listening device

Langan Neurology 2005;64:1131 (n=154)

Conclusions

- SUDEP is the most common epilepsy related cause of death and a major cause in chronic epilepsy
- Poor control of GTCS most important risk factor
- SUDEP in general in conjunction with a GTCS
  - But most patients with GTCS will not die in SUDEP
  - And most SUDEP victims have hade many non-fatal GTCS
- Final mechanisms unclear, probably multiple
- Possible preventive measures include
  - Improved drug treatment to reduce GTCS
  - Epilepsy surgery in suitable patients
  - Night time supervision in high risk patients
  - Adequate information

The Need for Awareness, Adequate Information and Counselling

Informing about SUDEP
When?
To whom?
How?

New Campaign to Shed Light on Epilepsy's Dark Secret

Awareness Campaign Champions More Research and More Action to Address Little Known Problem

TORONTO, May 11 - People with epilepsy can die suddenly and without warning. Families and friends are left in shock, with anger and frustration, searching for answers. Why don't we know more about this? Could we have done something to prevent this tragedy? How can we stop another unnecessary death?

Beginning today, the commitment to find some answers is strengthened - through the launch of a SUDEP awareness campaign

João Malva (Portugal)

THE NEUROGENIC NICHE DYNAMICS

Fernando Kok (Brazil)

MAIN INBORN ERRORS OF METABOLISM

Iscia Lopes Cendes (Brazil)

INVESTIGATING GENETIC SYNDROMES: MAIN ASPECTS

Investigating genetic syndromes: main aspects

Iscia Lopes Cendes
Professora Titular
Departamento de Genética Médica
FCM-UNICAMP

Definição de teste molecular

Uso de informação de genética molecular para: - elucidação diagnóstica em indivíduos já sintomáticos (TESTES DIÁGNÓSTICOS)

- predizer o início da doença em indivíduos em risco devido a história familial (TESTES PREDITIVOS) – Projeto diretrizes CFM/AMB (www.cfm.org.br)

Testes moleculares direto ao consumidor

- Testes para suscetibilidade a doenças complexas, características pessoais e ancestralidade comercializados diretamente aos consumidores, sem o envolvimento de profissionais de saúde, geralmente através da internet.
- QUESTÕES:
  - Validade de alguns resultados informados
  - ausência de aconselhamento genético
- ASHG *Position Statement**: necessidade maior regulação no setor, maior transparência , maior educação da população para os potenciais riscos

Benefícios Potenciais (TD)

- Elucida (confirma) o diagnóstico
- Proporcionar informação sobre prognóstico
- Pode evitar outros exames invasivos e dispendiosos
- Confirma a etiologia genética da doença
- Da subsídios para tomada de decisões reprodutivas

Riscos Potencias (TD)

- Conflitos emocionais (uma explicação genética é perturbadora ou reconfortante ?)
- Discriminação e estigma
  - *Genetic Information Nondiscrimination Act – GINA nos EUA, 2008*
- Efeitos negativos na dinâmica familiar e social

Teste Diagnóstico

Teste Molecular

- Reação ao resultado do teste molecular vai variar na dependência:
  - Contexto clínico (gravidade da doença, disponibilidade de tratamento)
  - Aspectos demográficos (idade, sexo, estágio da vida)
  - Valores culturais, religião, preferências pessoais

Processo de avaliação *ACCE*

Testes Moleculares:

Validade Analítica: O teste identifica o genótipo acuradamente?

Validade Clínica: O teste consegue informar se a pessoa tem ou não a doença (ou vai desenvolver a doença no futuro)?

Utilidade Clínica:Quais são os benefícios trazidos pelo teste no contexto clínico? Os benefícios são maiores do que os risco em potencial?

Aspectos Éticos, Legais e Sociais

Office of Public Health Genomics, CDC, and the Foundation for Blood Research (http://www.cdc.gov/genomics/gtesting/ACCE.htm).

Componentes da Validade Clínica

- **Sensibilidade:** Qual a proporção de indivíduos afetados que têm teste positivo?
- **Valor Preditivo positivo:** Qual a proporção dos indivíduos que testaram positivo têm a doença?
- **Valor preditivo negativo:** Qual a proporção dos indivíduos que testaram negativo não têm a doença?

	Teste Positivo	Teste Negativo
Afetado	Verdadeiro Positivo (VP)	Falso negativo (FN)
Não afetado	Falso positivo (FP)	Verdadeiro negativo (VN)

Fatores que influenciam a Validade Clínica

- Expressividade variável: mutações em um único gene pode levar a quadro clínico distinto. Fica dificultado o estabelecimento de prognóstico baseado na presença da mutação.
- Penetrância reduzida: alguns dos indivíduos que herdaram a mutação não apresentam a doença.
- Heteregeneidade de locus: uma mesma doença é causada por mutações em genes distintos, sendo que eu algumas famílias não se encontram mutações nos genes já descritos.

Considerações sobre a Utilidade Clínica

- O resultado do teste vai mudar os procedimentos usados para o diagnóstico (ex. dispensará exames mais invasivos?)
- O resultado do teste mudará a conduta terapêutica? ou terá impacto no estabelecimento do prognóstico?
- O resultado do teste poderá ter outra repercussão positiva sobre o pacientes? (psicológica por exemplo)

Validade Analítica

- Se refere ao componente laboratorial:
  - Sensibildiade analítica
  - Especificidade análitica
  - Controle de qualidade do laboratório
  - Reprodutibilidade dos resultados

Validade Analítica dos Testes Moleculares

- Mesmo quando um teste para uma alteração molecular específica em um gene especifico é acurado, esse mesmo teste pode não detectar outras alterações importantes para as quais ele não foi desenhado para detectar
- Nenhum teste disponível atualmente é capaz de detectar todas as alterações potencialmente deletérias em um determinado gene

Métodos Moleculares

- Triagem de mutações
- Sequenciamento de DNA
- Fluorescent in situ hybridization (FISH)
- Array-Comparative Genomic Hybridization (Array-CGH)
- Single nucleotide polymorphism arrays (SNP arrays)
- Multiplex ligation-dependent probe amplification (MLPA)
- Outros (análise de ligação, análise de metilação, teste da proteína truncada (PTT), estudo de dissomia uniparental (UPD), análise de Southern)

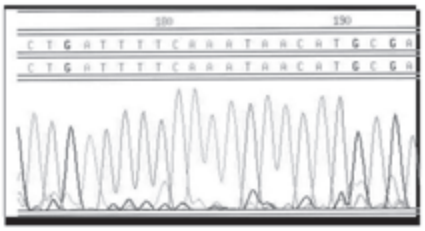
MLPA

Multiplex Ligation-dependent Probe Amplification

- Detecção de variações do número de cópias em regiões específicas
  - **Variação do número de cópias** (*Copy number variation - CNV*): segmentos do genoma (>1Kb) que apresentam diferenças no número de cópias em comparação com outro genoma

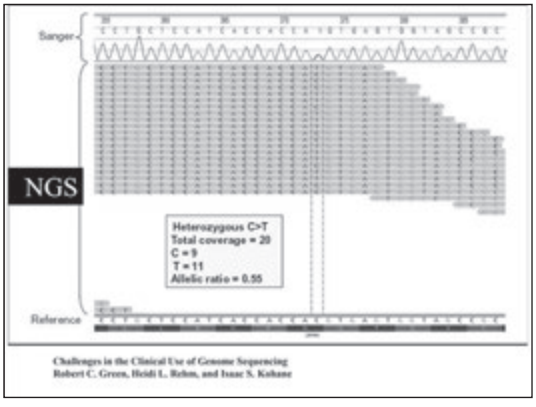
Frank et al, 2006

DNA sequencing



NGS

- J.Watson´s genome
- $ 1 million
- 454 platform (Roche)



Challenges in the Clinical Use of Genome Sequencing
Robert C. Green, Heidi L. Rehm, and Isaac S. Kohane

nature genetics

Exome sequencing identifies the cause of a mendelian disorder

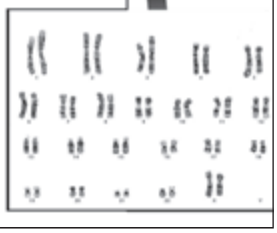
Sarah B Ng[1,10], Kati J Buckingham[2,10], Choli Lee[1], Abigail W Bigham[2], Holly K Tabor[2,3], Karin M Dent[4], Chad D Huff[5], Paul T Shannon[6], Ethylin Wang Jabs[7,8], Deborah A Nickerson[1], Jay Shendure[1] & Michael J Bamshad[2,3,9]

We demonstrate the first successful application of exome sequencing to discover the gene for a rare mendelian disorder of unknown cause, Miller syndrome (MIM%263750). For four affected individuals in three independent kindreds, we captured and sequenced coding regions to a mean coverage of 40× and sufficient depth to call variants at ~97% of each targeted exome. Filtering against public SNP databases and eight HapMap exomes for genes with two previously unknown variants in each of the four individuals identified a single candidate gene, *DHODH*, which encodes a key enzyme in the pyrimidine de novo biosynthesis pathway. Sanger sequencing confirmed the presence of *DHODH* mutations in three additional families with Miller syndrome. Exome sequencing of a small number of unrelated affected individuals is a powerful, efficient strategy for identifying the genes underlying rare mendelian disorders and will likely transform the genetic analysis of monogenic traits.

Testes Genéticos no Brasil

- **Genética Clínica**
- **40 anos**
- **Cariótipo**

SUS



SUS

Ministério da Saúde - MS
Secretaria de Atenção à Saúde
Tabela de Procedimentos, Medicamentos, Órteses, Próteses e Materiais Especiais do SUS

0202100030	DETERMINACAO DE CARIOTIPO EM SANGUE PERIFERICO (C/ TECNICA DE BANDAS)	32,48
0202110010	DETECCAO DE VARIANTES DA HEMOGLOBINA (DIAGNOSTICO TARDIO)	8,80
0202110028	DETECCAO MOLECULAR DE MUTACAO EM HEMOGLOBINOPATIAS (CONFIRMATORIO)	66,00
0202110036	DETECCAO MOLECULAR EM FIBROSE CISTICA (CONFIRMATORIO)	66,00
0202090045	TESTE DE GASTROACIDOGRAMA – SECRECAO BASAL POR 60 EM 4 AMOSTRAS	4,69
0202090053	TESTE DE HOLLANDER NO SUCO GASTRICO	4,69
0202100014	DETERMINACAO DE CARIOTIPO EM CULTURA DE LONGA DURACAO (C/ TECNICA DE BANDAS)	32,48
0202100022	DETERMINACAO DE CARIOTIPO EM MEDULA OSSEA E VILOSIDADES CORIONICAS (C/ TECNICA DE BANDAS)	32,48

ARTICLE

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

The American Journal of Human Genetics 86, 749–764, May 14, 2010

ELSEVIER

Seminars in Pediatric Neurology

Updates in the Genetic Evaluation of the Child with Global Developmental Delay or Intellectual Disability

Leigh Anne Flore, MD, and Jeff M. Milunsky, MD

Semin Pediatr Neurol 19:173-180 © 2

SHORT REPORT Open Access

Array CGH as a first line diagnostic test in place of karyotyping for postnatal referrals - results from four years' clinical application for over 8,700 patients

Genética

Procedimentos

Citogenética

Cariótipo com bandas, biópsia de pele ou outros tecidos

Cariótipo com bandas, material de aborto ou natimorto

Cariótipo com bandas, para doenças hematológicas, sangue periférico, tecidos fetóides e medula óssea

Cariótipo com bandas, sangue fetal

Cariótipo com bandas, sangue periférico

Cariótipo com bandas, vilosidades coriônicas

Cariótipo com pesquisa de troca de cromátides irmãs

Cariótipo com técnicas de alta resolução (estudo em prometáfase)

Cariótipo para síndromes de quebras cromossômicas, sangue periférico

Detecção de anormalidades dos cromossomos X ou Y, sangue periférico ou esfregaço de mucosa bucal, por FISH

Estudo citogenético para doenças neoplásicas malignas, diversos materiais

Líquido amniótico, cariótipo com bandas

Técnicas citogenéticas moleculares (fluorescence in situ hybridization – FISH) – de acordo com diretriz de utilização

Rol de Procedimentos e Eventos em Saúde

Resolução Normativa RN nº 167, de 9 de janeiro de 2008 e anexos

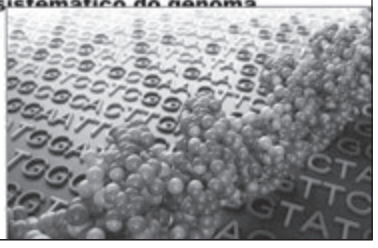
ANS Agência Nacional de Saúde Suplementar

Genética molecular

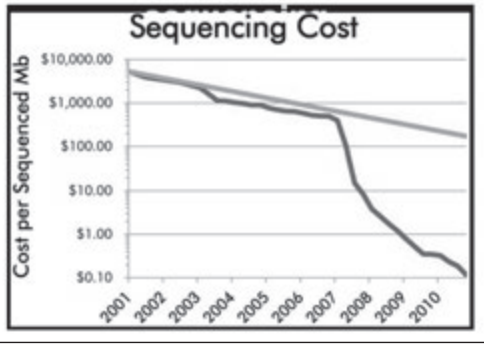
Análise molecular de DNA para doenças genéticas (de acordo com diretriz de utilização)

MEDICINA GENÔMICA

- 1987 – Mc Kusick e Ruddle
- Estudo sistemático do genoma humano

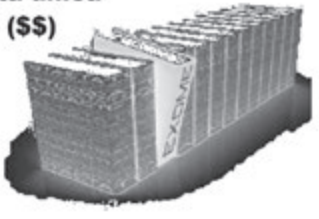


Next-generation



EXOMA

- 1 – 2%
- 85% variantes
- Coleta única
- WGS ($$)



ANÁLISE DE BIOINFORMÁTICA

- Algoritmos analíticos
- Modelo de doença

NEWS AND VIEWS

Exome sequencing makes medical genomics a reality

Leslie G Biesecke

Genetic diagnosis by whole exome capture and massively parallel DNA sequencing

New disease loci

ORIGINAL ARTICLE

Clinical application of exome sequencing in undiagnosed genetic conditions

Anna C Need,[1] Vandana Shashi,[2] Yuki Hitomi,[1] Kelly Schoch,[2] Kevin V Shianna,[1] Marie T McDonald,[2] Miriam H Meisler,[3] David B Goldstein[1,4]

Exome diagnostics: already a reality?

Constantin Polychronakos

Tech News

Genomics Moves into the Clinic

Diagnostic Exome Sequencing — Are We There Yet?

Heather C. Mefford, M.D., Ph.D.

CLINICAL GENETICS

Review

Next-generation sequencing: ready for the clinics?

AN Desai and A Jere

Comissão de Genética da ILAE

Membros(2006-2009):

Ruth Ottman, Ph.D., USA (Chair)
Shinichi Hirose, M.D., Ph.D., JAPAN
Satish Jain, M.D., D.M., F.R.C.P., INDIA
Holger Lerche, M.D., GERMANY
Iscia Lopes-Cendes, M.D., Ph.D., BRAZIL
Jeffrey L. Noebels, M.D., Ph.D., USA
Ingrid E. Scheffer, M.B.B.S. Ph.D. F.R.A.C.P., AUSTRALIA
José Serratosa, M.D., Ph.D., SPAIN
Federico Zara, Ph.D., ITALY

- Desenvolver um relatório sobre a aplicação clínica dos testes genéticos em epilepsia
- Resultado do trabalho foi publicado no periódico Epilepsia em abril de 2010.

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

Síndromes de epilepsia idiopática cujos genes já foram identificados

Syndromes beginning in the first year of life	LOCUS	GENE
Benign familial neonatal seizures	20q13 8q24	*KCNQ2* *KCNQ3*
Benign familial neonatal-infantile seizures	2q23-q24	*SCN2A*
X-linked infantile spasms	Xp22	*ARX*
Early-onset spasms	Xp22	*STK9/CDKL5*
Dravet syndrome, GEFS+, febrile seizures	**LOCUS**	**GENE**
Dravet syndrome (SMEI)	2q24	*SCN1A*
Genetic epilepsy with febrile seizures plus (GEFS+)	2q24 19q13 2q23-q24 5q34	*SCN1A* *SCN1B* *SCN2A* *GABRG2*
Childhood absence epilepsy with febrile seizures	5q34	*GABRG2*
Epilepsy limited to females with MR	Xq22	*PDH19*

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

Síndromes de epilepsia idiopática cujos genes já foram identificados

Idiopathic generalized epilepsies	LOCUS	GENE
Idiopathic generalized epilepsy	3q26-ter	*CLCN1*
Juvenile myoclonic epilepsy	5q34-q35 6p12-p11	*GABRA1* *EFHC1*
Focal epilepsies	**LOCUS**	**GENE**
AD nocturnal frontal lobe epilepsy	20q13 1q21 8p21	*CHRNA4* *CHRNB2* *CHRNA2*
AD partial epilepsy with auditory features (AD lateral temporal epilepsy)	10q24	*LGI1*

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

Síndromes de epilepsia idiopática cujos genes já foram identificados

Epilepsies associated with other paroxysmal disorders	LOCUS	GENE
Generalized epilepsy with paroxysmal dyskinesia	10q22	*KCNMA1*
Absence epilepsy and episodic ataxia	19p13	*CACNA1A*
Focal epilepsy and episodic ataxia	12p13	*KCNA1*
Familial hemiplegic migraine and epilepsy	1q21-23	*ATP1A2*

Genetic testing in the epilepsies--report of the ILAE Genetics Commission.
Ottman R, Hirose S, Jain S, Lerche H, Lopes-Cendes I, Noebels JL, Serratosa J, Zara F, Scheffer IE.
Epilepsia. 2010 Apr;51(4):655-70.

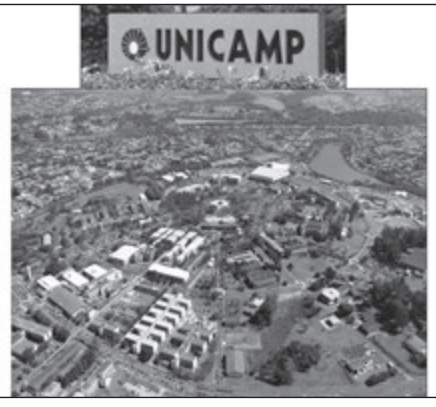
	Síndrome de Dravet (*SCN1A*)	GEFS+ (*SCN1A*)	ADPEAF/ADLTE (*LGI1*)
Contexto Clínico	Paciente com quadro clínico típico com apresentação clínica grave	História familial positiva (herança autossômica dominante)	História familial positiva (herança autossômica dominante)
Validade Clínica	Mutações do tipo *nonsense* (stop-codon) 80%	Teste positivo confirma, Teste negativo não exclui o diagnóstico	Teste positivo confirma, Teste negativo não exclui o diagnóstico
Utilidade Clínica	**ALTA** • Fecha o diagnóstico evitando outros exames • Auxilia na escolha do melhor tratamento • Tem implicações no aconselhamento genético (maioria casos esporádicos)	**BAIXA** • Grande variação na apresentação clínica, geralmente casos benignos • Presença de mutação não influencia diagnóstico ou tratamento • Pode ter implicações no AG	**BAIXA** • Doença benigna • Presença de mutação não influencia diagnóstico ou escolha terapêutica • Pode ter implicações no AG

Antes do Teste

- Testes moleculares devem ser precedidos de consentimento informado. Já que a informação genética é de natureza complexa e tem implicações profundas para o indivíduo e muitas vezes outros familiares.

Onde conseguir informação

- (www.genetests.org)



Jaime Carrizosa Moog (Colombia)

RETT SYNDROME

Síndrome de Rett

JAIME CARRIZOSA M.

Neurólogo Infantil
Universidad de Antioquia
Medellín-Colombia

LASSE VIII - 2014

TRASTORNOS GENERALIZADOS DEL DESARROLLO DSM IV

- TRASTORNO AUTISTA
- TRASTORNO DE RETT
- TRASTORNO DESINTEGRATIVO INFANTIL
- TRASTORNO DE ASPERGER
- TRASTORNO GENERALIZADO DEL DESARROLLO NO ESPECIFICADO

FRECUENCIA

1:10000 MUJERES NACIDAS VIVAS
1:15000 MUJERES NACIDAS VIVAS

HERENCIA LIGADA AL CROMOSOMA X DOMINANTE

SÍNDROME DE RETT – CRITERIOS DIAGNÓSTICOS

A. Todas las características siguientes:

- desarrollo prenatal y perinatal aparentemente normal.
- desarrollo psicomotor aparentemente normal durante los primeros 5 meses después del nacimiento.
- circunferencia craneal normal en el nacimiento.

SÍNDROME DE RETT – CRITERIOS DIAGNÓSTICOS

B. Aparición de todas las características siguientes después del período de desarrollo normal:

- desaceleración del crecimiento craneal entre los 5 y 48 meses de edad.
- pérdida de habilidades manuales intencionales previamente adquiridas entre los 5 y 30 meses de edad, con el subsiguiente desarrollo de movimientos manuales estereotipados (p. ej., escribir o lavarse las manos).

SÍNDROME DE RETT – CRITERIOS DIAGNÓSTICOS

- pérdida de implicación social en el inicio del trastorno (aunque con frecuencia la interacción social se desarrolla posteriormente).
- mala coordinación de la marcha o de los movimientos del tronco.
- desarrollo del lenguaje expresivo y receptivo gravemente afectado, con retraso psicomotor grave.

ESTADÍOS CLÍNICOS

ESTADÍO 1

- ESTANCAMIENTO DEL DESARROLLO PSICOMOTOR ENTRE LOS 6 A 18 MESES
- DESACELERACIÓN DEL CRECIMIENTO DEL PERÍMETRO CEFÁLICO
- HIPOTONÍA MUSCULAR
- DESINTERÉS POR EL JUEGO

ESTADÍOS CLÍNICOS

ESTADÍO 2

- ENTRE 2 Y 3 AÑO REGRESIÓN PSICOMOTORA RÁPIDA
- IRRITABILIDAD
- ESTEREOTIPIAS MANUALES
- PÉRDIDA DEL USO PROPOSITIVO DE LAS MANOS
- PÉRDIDA DEL LENGUAJE
- SIGNOS AUTISTAS

ESTADÍOS CLÍNICOS

ESTADÍO 3

Entre los 2 a 10 años presenta retardo mental con rasgos autistas, desconexión social, estereotipias de las manos, ataxia, apraxia, trastornos respiratorios, escoliosis y convulsiones

ESTADÍOS CLÍNICOS

ESTADÍO 4

Posterior a los 10 años con signos de neurona motora superior e inferior que limitan la marcha, defectos tróficos de manos y pies, escoliosis y disminución de las convulsiones

CONVULSIONES

Prácticamente casi todas las pacientes tienen alteraciones electroencefalográficas consistentes en:

- Espigas y ondas agudas posteriores
- Espigas y ondas agudas durante el sueño

Cerca del 30% tienen crisis epilépticas

ETIOLOGÍA

LOCUS Xq28 GEN MECP2

LOCUS Xp22 GEN CDKL5

HERENCIA LIGADA AL CROMOSOMA X DOMINANTE ESPORÁDICO

MÁS DE 2000 MUTACIONES IDENTIFICADAS

GENÉTICA

MECP2 CODIFICA LA PROTEINA 2 METILADA LIGADORA CpG

ESTA PROTEINA SE UNE SELECTIVAMENTE AL DNA METILADO Y REGULA LA PREPRESIÓN TRANSCRIPCIONAL.

LA PROTEINA INTERACTÚA CON DEACETILASAS DE HISTONAS Y EL COMPLEJO CORREPRESOR Sin3A

GENÉTICA

LA DEACETILACIÓN DE LAS HISTONAS PASAN LA CROMATINA DE UNA FORMA ACTIVA A INACTIVA

MECP2 SE EXPRESA Y ES ABUNDANTE EN EL CEREBRO.

PATOLOGÍA

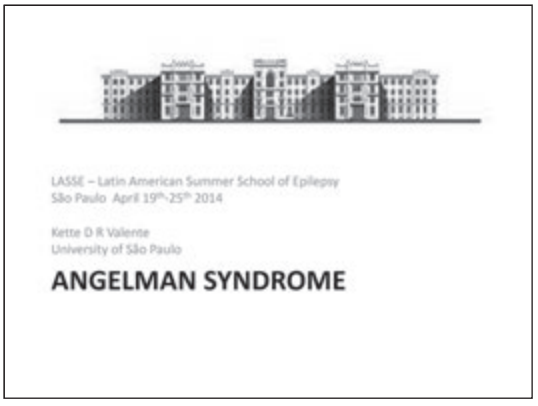
- ATROFIA CEREBRAL DIFUSA
- ACÚMULO DE LIPOFUSCINA
- HIPOPIGMENTACIÓN SUSTANCIA NIGRA
- REDUCCIÓN TAMAÑO NEURONAL
- DISMINUCIÓN DENDRITAS Y ARBORIZACIÓN NEURONAL EN CORTEZA FRONTAL Y LÍMBICA
- DISMINUCIÓN CÉLULAS DE PURKINJE CEREBELOSAS

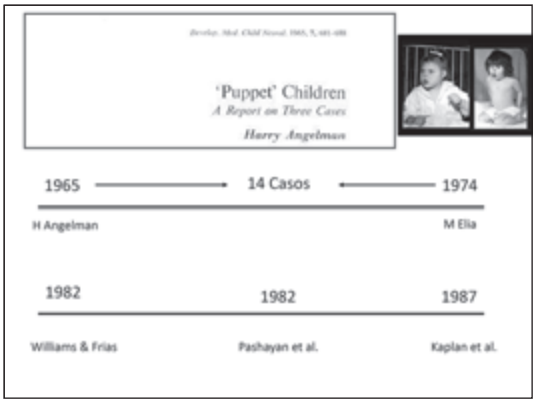
TRATAMIENTO

- TERAPIAS FÍSICA, LENGUAJE, OCUPACIONAL
- TRATAMIENTO ANTICONVULSIVANTE

KETTE VALENTE (BRAZIL)

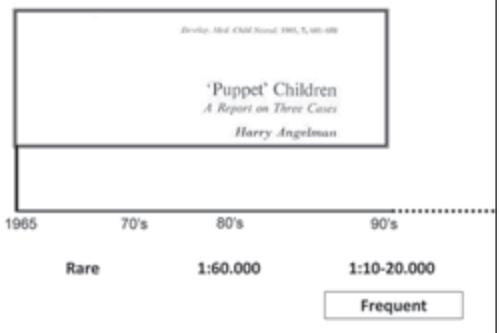
ANGELMAN SYNDROME

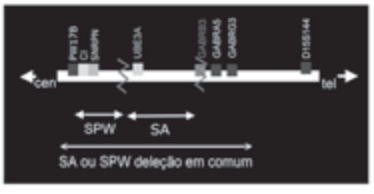




Case Series: Phenotype delineation

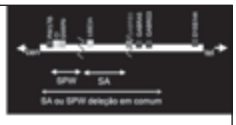
Year	Author	Number of Patients	Country
1989	Robb et al.	36	UK
1992	Zori et al.	75	USA
1993	Clayton-Smith	82	UK
1994	Saitoh et al.	61	Japan
1995	Buntinx et al.	47	Netherlands





GENETIC MECHANISMS

Genetic Mechanisms

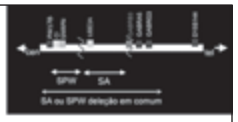


Deletion

Kaplan et al., 1987
Magenis et al., 1987

Frequency: 60-70%
Risk of Recurrence: 0 a 1%

Genetic Mechanisms

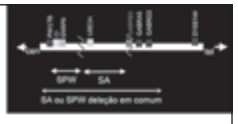


UPD maternal

Malcolm et al., 1991
Knoll et al., 1991

Frequency: 1-2%
Risk of Recurrence: 0 a 1%

Genetic Mechanisms

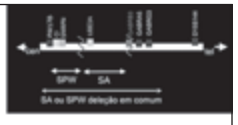


Imprinting Center Abnormalities

Dittrich et al., 1992
Glenn et al., 1993

Frequency: 2-5%
Risk of Recurrence: 0 a 50%

Genetic Mechanisms



UBE3A mutation

Kishino et al., 1997
Matsuura et al., 1997

Frequency: 5-8%
Risk of Recurrence: 0 a 50%

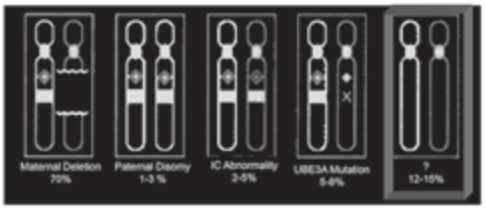
Genetic Test in AS

1.	Characteristic AS pattern of DNA methylation of the *SNURF-SNRPN* exon 1/promoter. Detects cases due to 15q11.2-q13 deletion, UPD, and IDs (may have mosaic methylation pattern in non-deletion IDs)
2.	Abnormal FISH indicating a deletion of 15q11.2-q13 DNA sequences within the common AS deletion overlap region. Use of a pericentromeric FISH probe enhances the ability to detect subtle translocation. Array-CGH can be used to detect the deletion but confirmation by FISH is currently required. Class I and II deletions can be distinguished by array-CGH or FISH using appropriate clones
3.	DNA polymorphism analysis within 15q11.2-q13 showing paternal UPD
4.	Deletion in the Imprinting Center, demonstrated by real-time PCR, single copy FISH, or other analysis methods of the AS Imprinting Center smallest region of overlap (SRO)
5.	Pathogenic DNA sequence change in the *UBE3A* gene

AS, Angelman syndrome; UPD, uniparental disomy; FISH, Fluorescence in situ hybridization; CGH, comparative genomic hybridization; sc, single copy; ID, imprinting defect; PCR, polymerase chain reaction.

Williams et al. 2005

Genetic Mechanisms



Angelman Syndrome Diagnosis

American Journal of Medical Genetics 140A:413–418 (2006)

Conference Report

Angelman Syndrome 2005: Updated Consensus for Diagnostic Criteria

Charles A. Williams,[1,2]* Arthur L. Beaudet,[2,3] Jill Clayton-Smith,[4] Joan H. Knoll,[5] Martin Kyllerman,[6] Laura A. Laan,[7] R. Ellyn Magenis,[8] Ann Moncla,[9] Albert A. Schinzel,[10] Jane A. Summers,[11] and Joseph Wagstaff[2,12]

CLINICAL FEATURES

American Journal of Medical Genetics 140A:413–418 (2006)

Conference Report

Angelman Syndrome 2005: Updated Consensus for Diagnostic Criteria

TABLE I. 2005: Developmental History and Laboratory Findings in AS*

1. Normal prenatal and birth history with normal head circumference and absence of major birth defects. Feeding difficulties may be present in the neonate and infant
2. Developmental delay evident by 6–12 months of age, sometimes associated with truncal hypotonia. Unsteady limb movements and/or increased smiling may be evident
3. Delayed but forward progression of development (no loss of skills)
4. Normal metabolic, hematologic, and chemical laboratory profiles
5. Structurally normal brain using MRI or CT (may have mild cortical atrophy or dysmyelination)

*These findings are useful as inclusion criteria but deviations should not exclude diagnosis.

American Journal of Medical Genetics 140A:413–418 (2006)

Conference Report

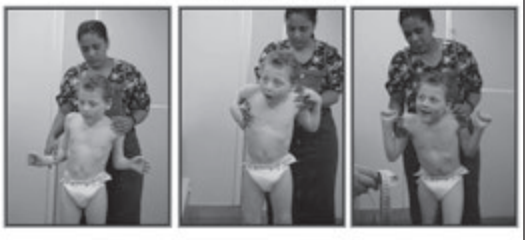
Angelman Syndrome 2005: Updated Consensus for Diagnostic Criteria

Consistent Criteria (100%)

Frequent Criteria (> 80%)

Associated Criteria (20 to 80%)

Consistent Criteria



Developmental Delay (Severe-Moderate)
Speech (Language) Impairment

"Movement Disorders" | *Wide-based gait*
Jerky movements

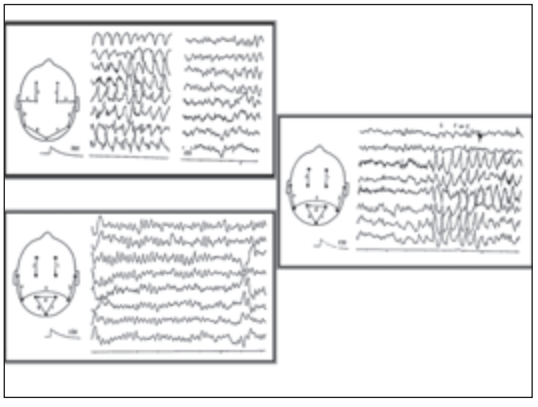
Robot like gait

Peculiar Behavior | Unprovoked laughter
Hand Flapping

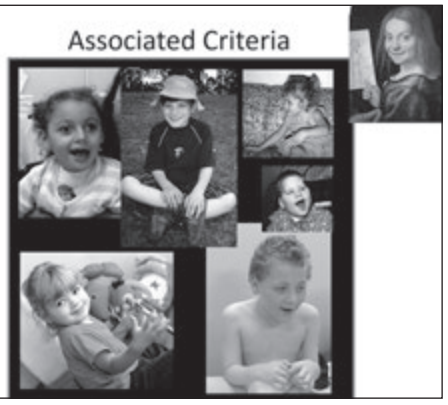
Happy demeanor in AS: An early diagnostic sign

Frequent Criteria

Microcephaly/ Brachycephaly
Epilepsy
Suggestive EEG Features



Associated Criteria



Hypopigmentation or Albinism Type II
(Pseudoalbinism)

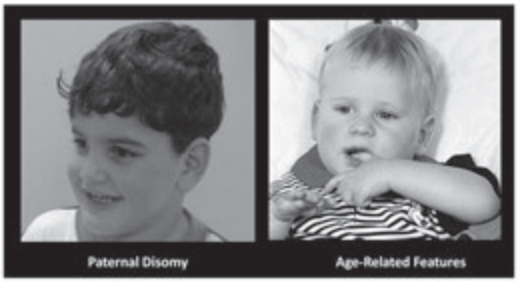
Hyperactivity/ Sleep Disorders

Water attraction

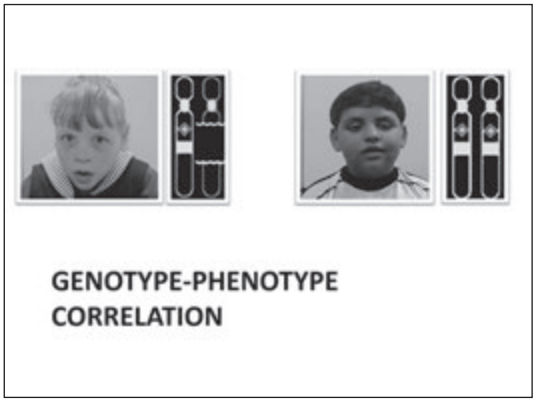
Oral motor behavior

Drooling

Unspecific features

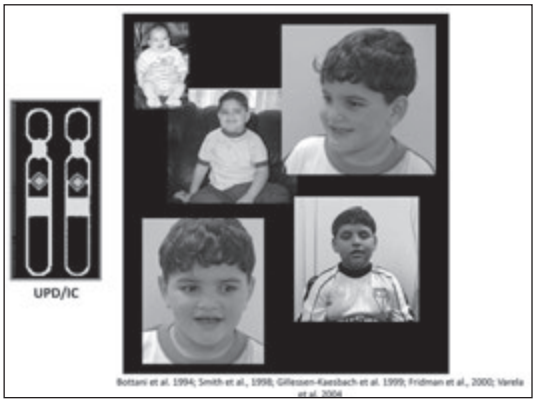


EVOLUTIONARY ASPECTS

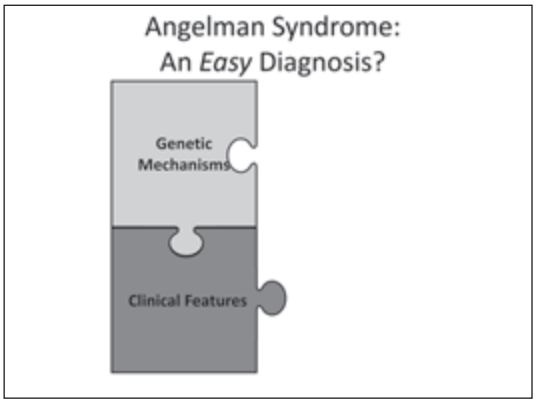

GENOTYPE-PHENOTYPE
CORRELATION


Deletion

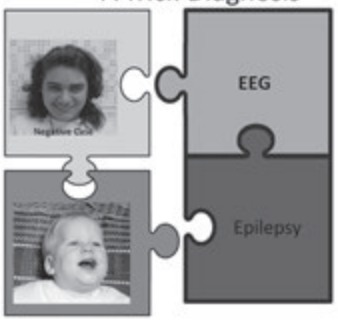

Deletion
BP1 – BP3 deletion
BP2 – BP3 deletion
Varela et al. 2004

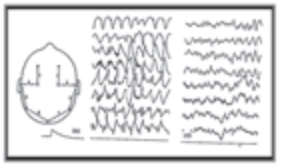

UPD/IC
Bottani et al. 1994; Smith et al., 1998; Gillessen-Kaesbach et al. 1999; Fridman et al., 2000; Varela et al. 2004


UBE3A
Moncla et al., 1999
Saitoh et al., 1999


Angelman Syndrome:
An *Easy* Diagnosis?
Genetic Mechanisms
Clinical Features

Angelman Syndrome: A *Trick* Diagnosis

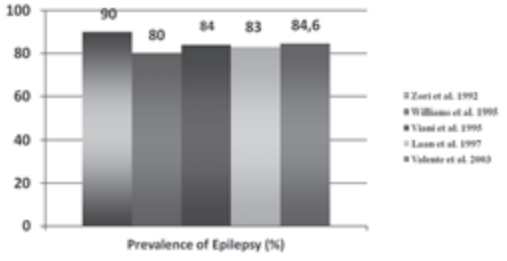




ELECTROCLINICAL FEATURES

THE RELEVANCE OF EPILEPSY AND EEG PATTERNS

Prevalence of Epilepsy



Epilepsy in AS

Periods with cognitive decline

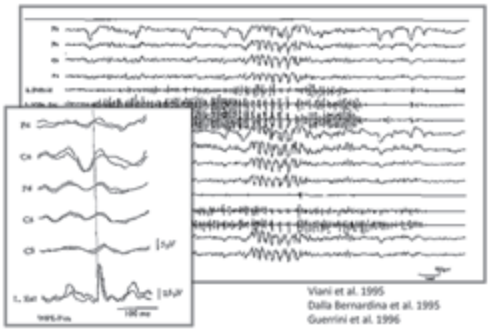
Atypical absence status with repetitive head nodding

Sugimoto et al., 1992
Minassian et al. 1998
Laan et al. 1997
Minassian et al. 1998

Atypical absence status occurred in 100%

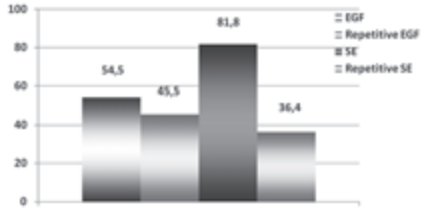
Matsumoto et al., 1992

Epilepsy in AS



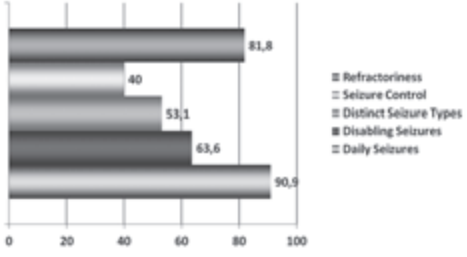
Viani et al. 1995
Dalla Bernardina et al. 1995
Guerrini et al. 1996

Epilepsy Aggravated by Fever and *Status Epilepticus*



Valente et al. 2003

Severity of Epilepsy



Epilepsy in Angelman Syndrome

High prevalence

Chronic encephalopathy with myoclonic status

Dalla Bernardina et al. 1995; Viani et al. 1995

Suggestive features that may guide the diagnosis

Generalized Epilepsy – AA; Myoclonic and GTC seizures

Epilepsy aggravated by fever

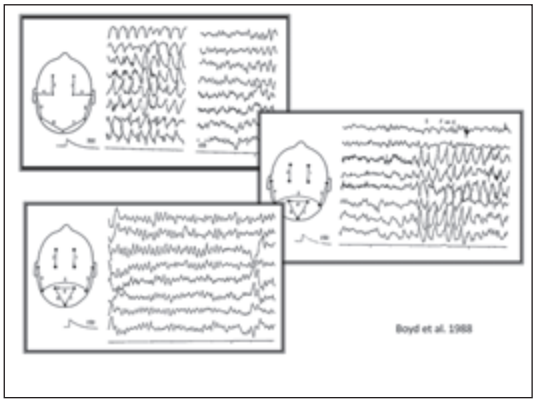
Non convulsive *SE*

Refractoriness

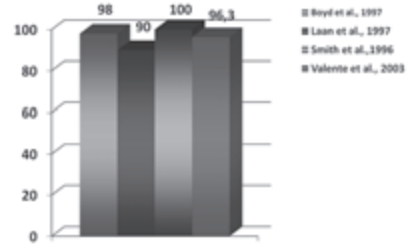
Sugimoto et al. 1992; Matsumoto et al. 1992; Dalla Bernardina et al. 1995; Viani et al. 1995; Guerrini et al. 1996; Laan et al. 1997

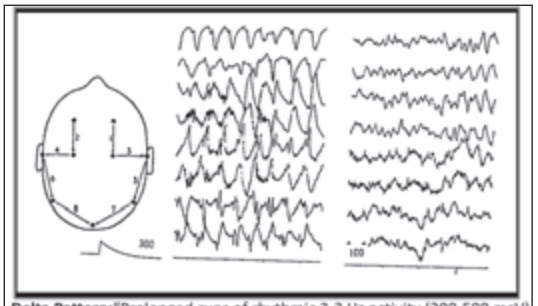
Treating epilepsy in Angelman Syndrome: Special considerations

Valproic Acid	Vigabatrin
Benzodiazepines	Phenytoin
Clonazepam	Lamotrigine
Ethosuximide	Carbamazepine
Topiramate	Oxcarbazepine
Ketogenic Diet	



Prevalence of suggestive EEG paterns





Delta Pattern: "Prolonged runs of rhythmic 2-3 Hz activity (200-500 mcV) often more prominent anteriorly, sometimes associated with epileptiform discharges (ill-defined spike/wave complexes) (13/19 patients)."

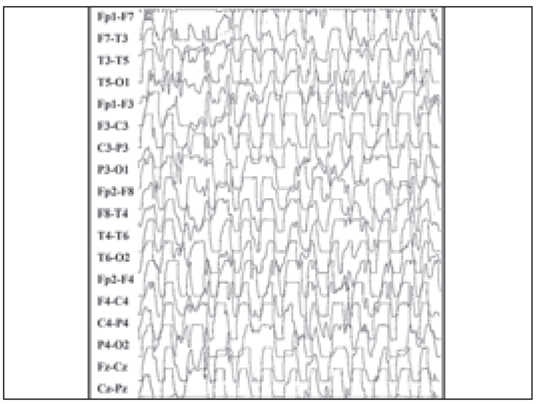
Terms used to denominate EEG patterns of AS

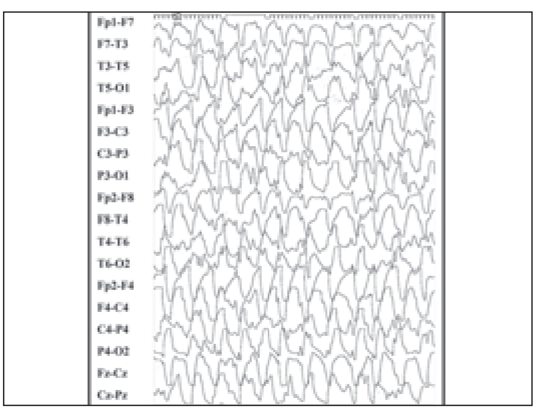
Triphasic pattern or activity
Laan et al. 1997; 1998

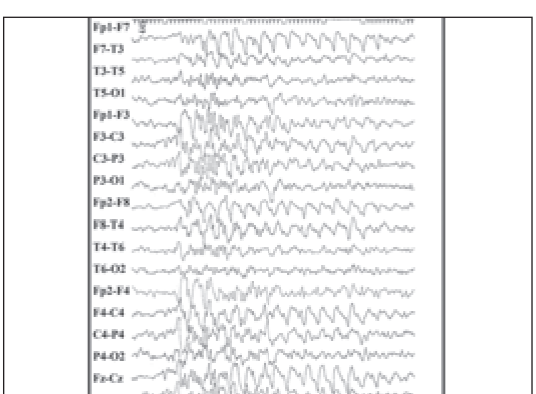
Ill-defined slow spike-and-wave complexes
Boyd et al. 1988

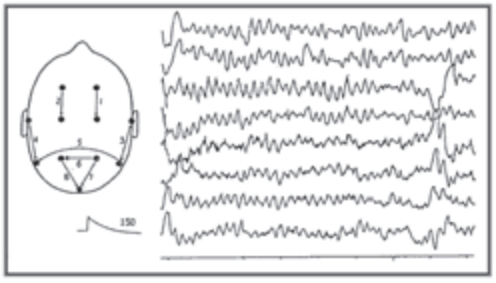
Hypsarrhythmic-like pattern
Matsumoto et al. 1992

Lennox-Gastaut like pattern
Matsumoto et al. 1992

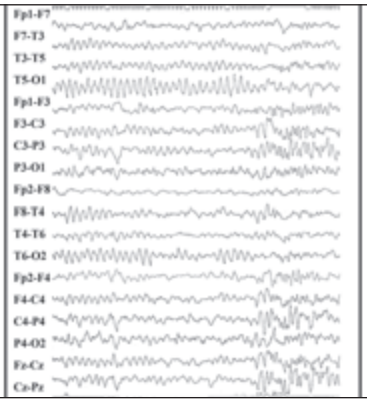


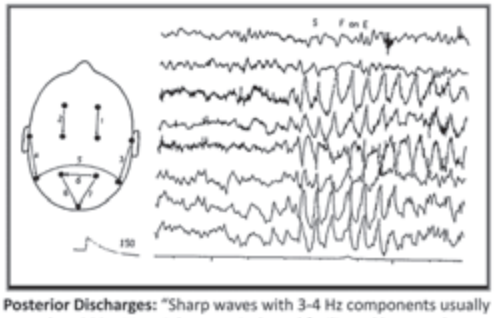




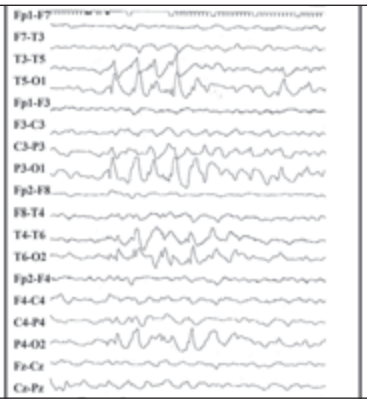


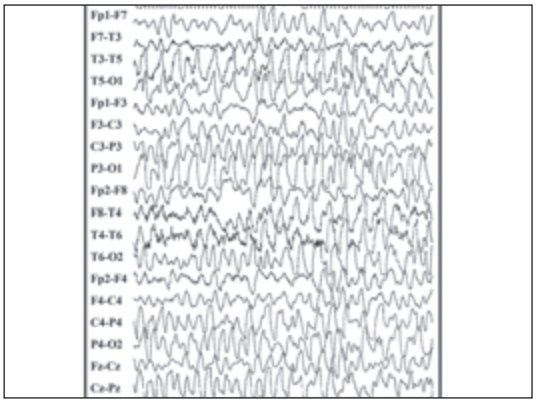
Theta Pattern: "Persistent rhythmic 4-6 Hz activities reaching more than 200 mV not associated with drowsiness (9 /19 patients)."

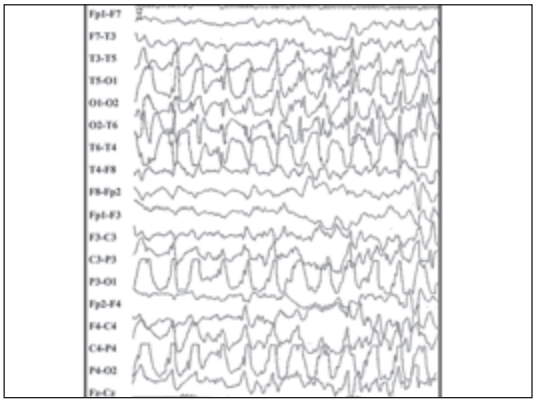


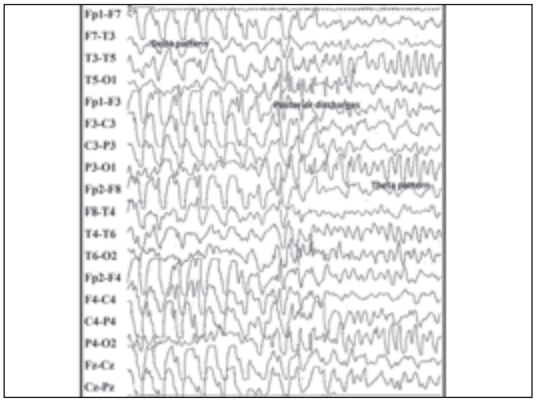


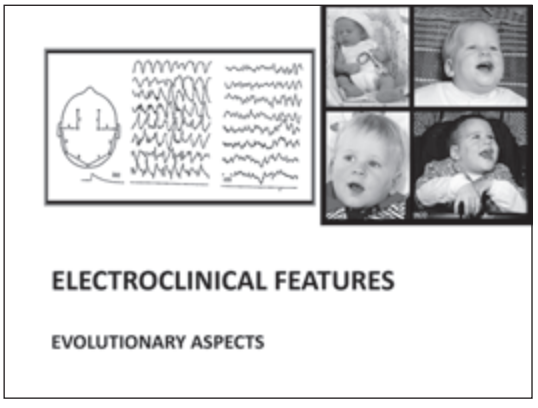
Posterior Discharges: "Sharp waves with 3-4 Hz components usually more than 200 mV, mainly posteriorly and facilitated by, or only seen with, eye closure. (17/19 patients)."

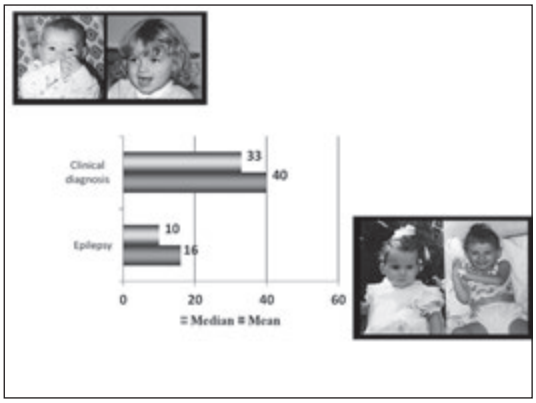



Fp1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz


Fp1-F7
F7-T3
T3-T5
T5-O1
O1-O2
O2-T6
T6-T4
T4-F8
F8-Fp2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz


Fp1-F7
F7-T3
T3-T5
T5-O1
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz


ELECTROCLINICAL FEATURES
EVOLUTIONARY ASPECTS



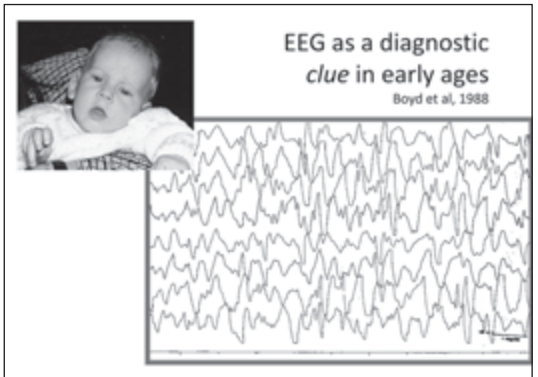
Epilepsy: Evolutionary Aspects

Age of onset: Infancy and Early Childhood
10-36 months

***Storm* period:** Early Childhood *x* Late Childhood/Adolescence

Age of Remission: Late Adolescence and Adulthood
Atypical absences and myoclonic seizures may persist

Boyd et al. 1988; Matsumoto et al. 1992; Clayton-Smith J 1993; Viani et al. 1995; Buoni et al. 1999
Buntinx et al., 1995; Laan et al., 1998



EEG as a diagnostic *clue* in early ages

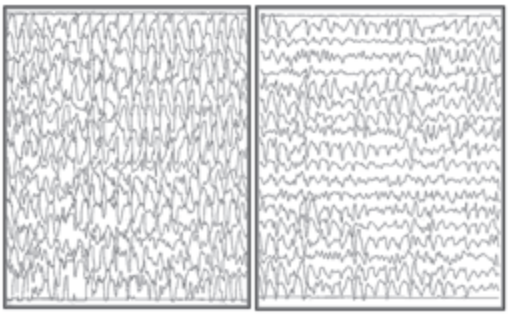
Boyd et al, 1988

Evolution of EEG Findings

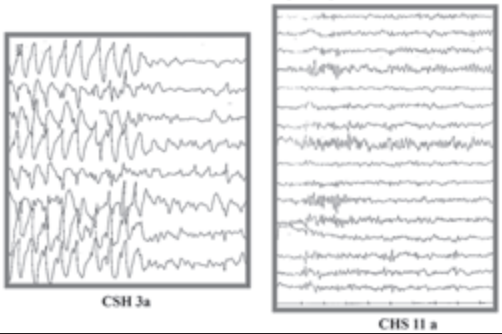
- Suggestive EEG patterns preceded the genetic diagnosis in 16 (72.7%)
- 15 patients who had EEGs prior to the clinical diagnosis - 9 (60%) with suggestive EEG

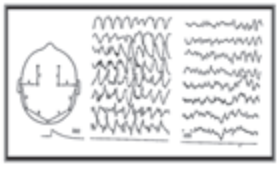
Laan et al. 1998
Valente et al. 2003
Valente et al. 2013

EEG: Evolutionary Aspects



EEG: Evolutionary Aspects





ELECTROCLINICAL FEATURES

GENTOYPE-PHENOTYPE CORRELATION

Epilepsy Phenotype-Genotype Correlation

Patients with deletion
13 patients

Severe intractable epilepsy, most frequently with atypical absences and myoclonias and less frequently with generalized extensor tonic seizures or flexor spasms.

Patients without deletion
UPD, ICA, UBE3A aged-matched
7 patients

No epilepsy or drug-responsive mild epilepsy with relatively infrequent atypical absences, myoclonias, or atonic seizures.

Minassian BA, DeLorey TM, Olsen RW, Philippart M, Bronstein Y, Zhang G, Guerrini R, Van Ness P, Livet MO, Delgado-Escueta AV. Angelman syndrome: correlations between epilepsy phenotypes and genotypes. Ann Neurol. 1998 Apr;43(4):485-93.

$GABA_A$ Receptors

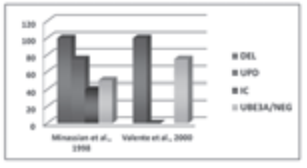
Deletion → **Severe Epilepsy**

Non-Deletion → **Milder Epilepsy**

Angelman syndrome: correlations between epilepsy phenotypes and genotypes.
Minassian BA; DeLorey TM; Olsen RW; *et al. Ann. Neurol. 1998; 43(4):485-93.*

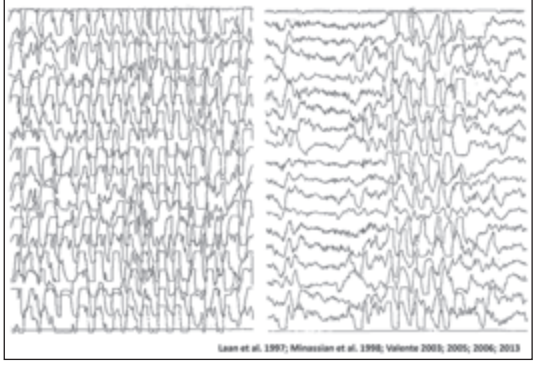
Arch Neurol. 2006;63:122-128

Epilepsy in Patients With Angelman Syndrome Caused by Deletion of the Chromosome 15q11-13

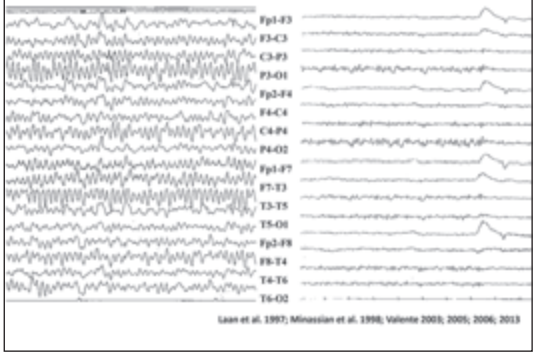


Epilepsy Research 67 (2005) 163–168

Angelman syndrome: Unparental paternal disomy 15 determines mild epilepsy, but has no influence on EEG patterns



Laan et al. 1997; Minassian et al. 1998; Valente 2003; 2005; 2006; 2013



Laan et al. 1997; Minassian et al. 1998; Valente 2003; 2005; 2006; 2013

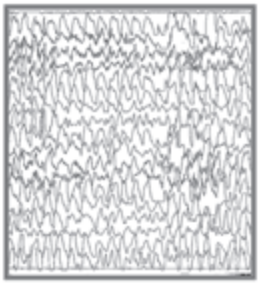
Conclusions

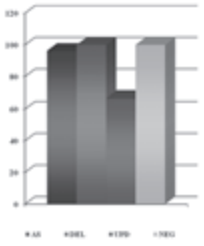
Intractable epilepsy in early childhood, especially in infants, with developmental delay should suggest AS.

Sugimoto et al., 1992
Matsumoto et al., 1992

Take home message: Epileptic encephalopathy in a child with developmental delay

Conclusions





EEG: A key finding for the diagnosis

The presence of highly suggestive patterns may guide the diagnosis

Boyd et al., 1988; Buoni et al., 2000

EEG patterns present an early onset compared to the phenotype which may guide the earlier diagnosis

EEG patterns are helpful for the identification of AS in all patients whatever the genetic mechanism.

HELEN SCHARFMAN (USA)

SEIZURES IN ALZHEIMER'S DISEASE

FERNANDO CENDES (BRAZIL)

NEUROIMAGING IN BRAIN MALFORMATIONS RELATED TO EPILEPSY

Ressonância Magnética
Malformações corticais

Fernando Cendes
Departamento de Neurologia
FCM - UNICAMP

Desenvolvimento cerebral e malformações congênitas

Desenvolvimento cerebral

- A embriologia do SNC é complexa e ordenada
- O desenvolvimento somático e psíquico depende do SNC
- A melhor compreensão dos processos e etapas do desenvolvimento normal e anormal do SNC poderá esclarecer os mecanismos envolvidos em diversas patologias

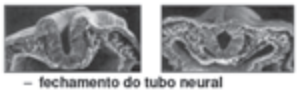
Desenvolvimento cerebral

- **1. Eventos precoces**
  - neurulação (formação da placa neural, pregas)
  - fechamento do tubo neural
  - formação das vesículas primitivas
  - Flexura cefálica
  - separação do ectoderma superficial e neuroectoderma
  - diverticulação e clivagem formando o prosencéfalo, mesencéfalo e robencéfalo

Desenvolvimento cerebral

- **1. Eventos precoces**

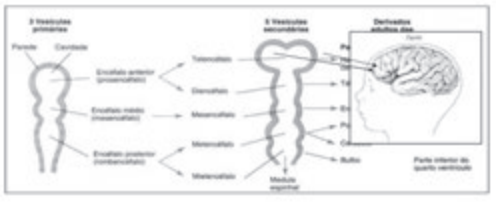
- neurulação (formação da placa neural, pregas)



- fechamento do tubo neural
- formação das vesículas primitivas; Flexura cefálica
- separação do ectoderma superficial e neuroectoderma

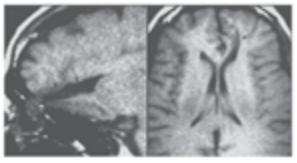
Desenvolvimento cerebral precoce

- **O tubo neural fecha aproximadamente no 24º dia de gestação**
- **A seguir, o prosencéfalo, na porção rostral do tubo neural, divide-se em**
  - **diencéfalo**
    - tálamo, hipotálamo, e globo pálido
  - **teléncefalo**
    - hemisférios cerebrais, putâmen e núcleo caudato



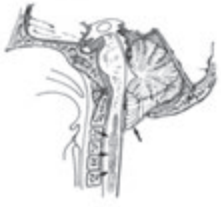
Desordens do fechamento do tubo neural
3ª e 4ª semanas de gestação

- **Cefaloceles**
  - **são protrusões de estruturas intracranianas através de defeitos da dura e calota óssea ("hérnias cerebrais")**



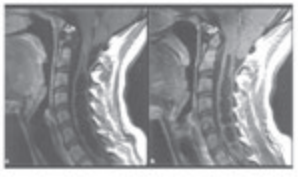
Malformações tipo Chiari

Chiari tipo I

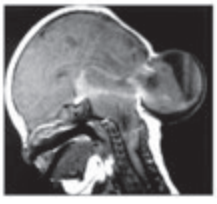


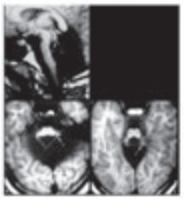
Chiari tipo II
(Arnold-Chiari and Cleland-Chiari)

Chiari I associada a seringomielia



Chiari tipo III e tipo IV

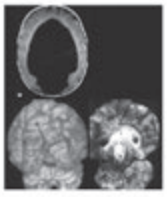




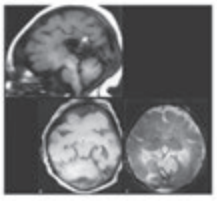
Holoprosencefalias

- **Incapacidade do prosencéfalo de se dividir em hemisférios ou lobos**
- **Constituem um grupo de desordens (*espectro*) caracterizadas por hipoplasia ou aplasia do segmento rostral do tubo neural e segmento premaxilar da face (ciclopia, fenda palatina)**

Holoprosencefalias

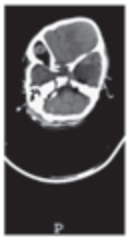


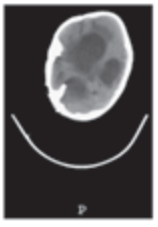
Holoprosencefalia alobar



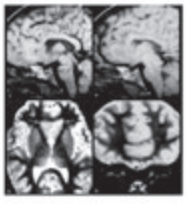
Holoprosencefalia semilobar

Holoprosencefalia

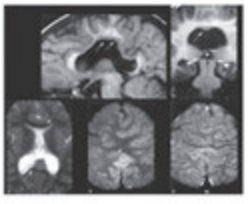




Holoprosencefalias

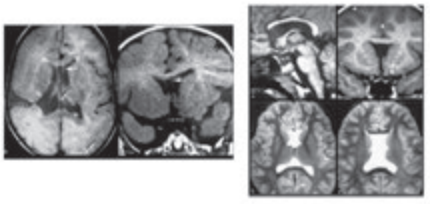


Holoprosencefalia lobar



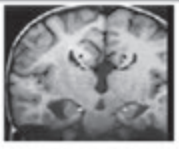
Holoprosencefalia lobar dorsal

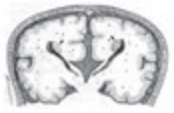
Displasia septo-óptica

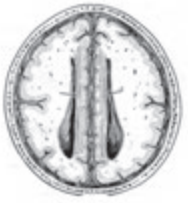


Agenesia do Corpo Caloso

entre 8 e 20 semanas de gestação





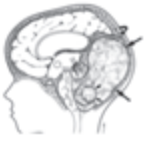


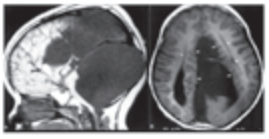
Agenesia completa de corpo caloso - feixes de Probst

Malformações da fossa posterior

Complexo Dandy-Walker

- Espectro de malformações da fossa posterior
- Clássica tríade
  - agenesia completa ou parcial do verme
  - Dilatação do IV ventrículo
  - Alargamento da fossa posterior
- Provavelmente resulta de um insulto intrauterino afetando o cerebelo e IV ventrículo

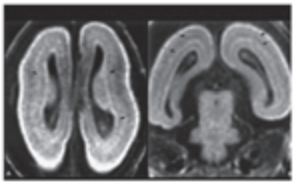




Desenvolvimento cerebral

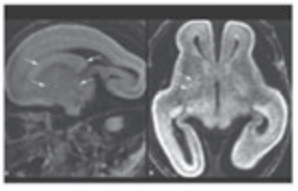
- **2. Entre 2 e 5 meses**
  - **formação da matriz germinativa**
  - **migração de neurônios da região subependimária ao córtex**
  - **formação de sulcos e giros cerebrais**
  - **formação das fibras comissurais (corpo caloso, etc)**
- **Terceiro trimestre => adulto**
  - **mielinização e função**
    - sentido caudal para cefálico, dorsal para ventral, central para periférico, sensorial antes do motor

Cérebro fetal, 14 semanas de gestação



imagens (axial e coronal - 3D GRE) obtidas de uma preparação anatômica, mostram cérebro liso sem o desenvolvimento de sulcos. Observe a matriz germinativa (setas, A) e migração de neurônios (setas, B)

Cérebro fetal, 14 semanas de gestação

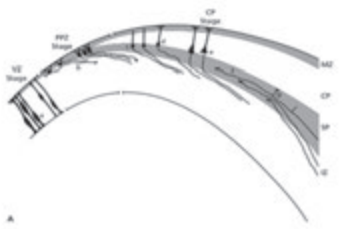


Condensação de neurônios primitivos do futuro núcleo caudato e núcleo lenticular

Distúrbios do desenvolvimento cortical

- **Proliferação**
- **Migração**
- **Organização**

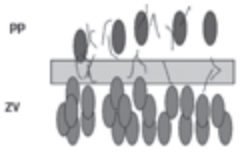
Formação do manto cortical



Desenvolvimento cortical

Proliferação e diferenciação neuroglial

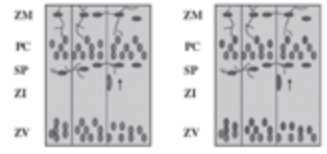
✓ precursores proliferam na Zona Ventricular (ZV)



4/5ª até 17/18ª semanas

Desenvolvimento cortical

Migração

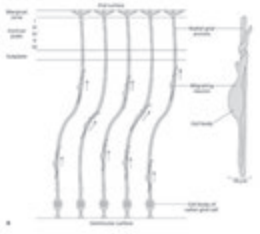


6/7ª até 20/24ª semanas

✓migração radial — células da glia

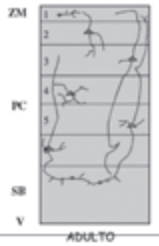
✓padrão *inside/out*

Formação da placa cortical

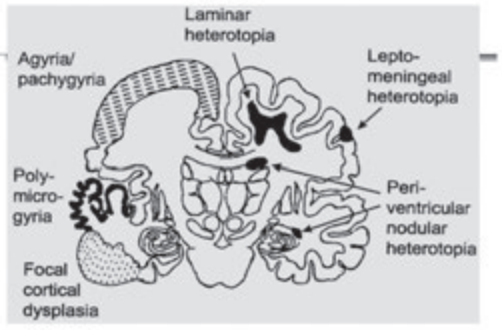


Desenvolvimento cortical

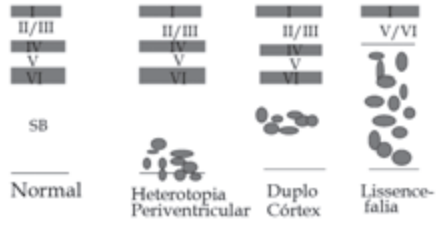
Organização



ADULTO



Estrutura do Córtex Displásico



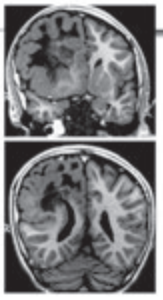
Distúrbio do desenvolvimento cortical

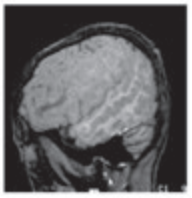
- **Proliferação**
  - **células primordiais sofrem mitoses assimétricas**
    - uma célula persiste com propriedades da célula primordial e a outra assume características de neuroblastos
  - **Período : 4ª a 5ª semanas até 17/18ª semanas**

Distúrbios da proliferação neuronal

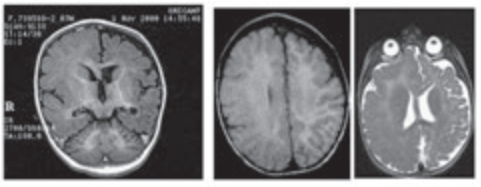
- **não neoplásico**
  - hemimegalencefalia **(isolada ou em síndromes neurocutâneas)**
  - displasia cortical focal **com células em balão**
  - **esclerose tuberosa**
- **neoplásicos (associada à desorganização cortical)**
  - **DNT**
  - **ganglioglioma, gangliocitoma**

Hemimegalencefalia

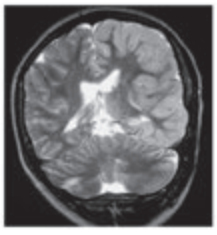




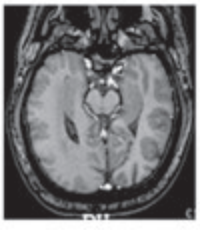
Hemimegalencefalia

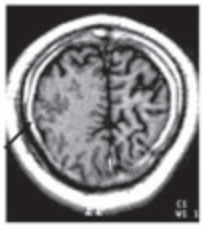


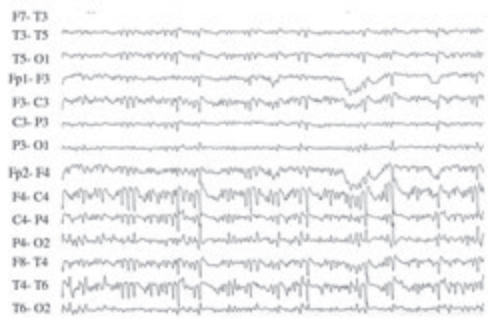
Hemimegalencefalia



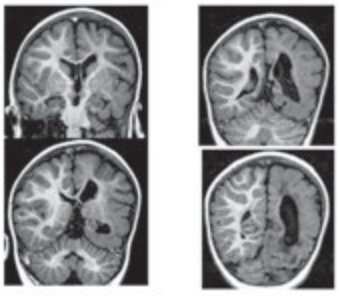
Hemimegalencefalia







Hemimegalencefalia - 2anos; Crises desde o nascimento



Epilepsia, 52(1):158–174, 2011
doi: 10.1111/j.1528-1167.2010.02777.x

SPECIAL REPORT

The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

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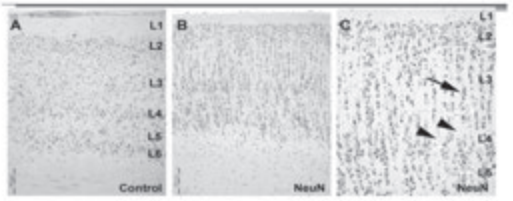
Revised three-tiered classification system for FCDs

FCD Type I (isolated)	*Focal Cortical Dysplasia with abnormal radial cortical lamination* (FCD Type IA)		*Focal Cortical Dysplasia with abnormal tangential cortical lamination* (FCD Type IB)	
FCD Type II (isolated)	*Focal Cortical Dysplasia with dysmorphic neurons* (FCD Type IIA)		*Focal Cortical Dysplasia with dysmorphic neurons and balloon cells* (FCD Type IIB)	
	FCD Type IA/IB may always be visible in adjacent cortex			
FCD Type III (associated with principal lesion)	FCD Type IIIA *Focal Cortical Dysplasia in the temporal lobe associated with mesial temporal sclerosis (MTS)*	FCD Type IIIB *Focal Cortical Dysplasia associated with a glial or glio-neuronal tumor*	FCD Type IIIC *Focal Cortical Dysplasia associated with vascular malformation or scar/porus*	FCD Type IIID *Focal Cortical Dysplasia associated with any other principal lesion*

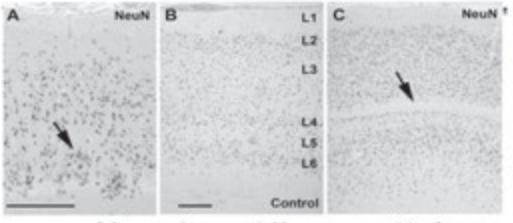
FCD Type III (not otherwise specified, NOS): if clinically/radiologically suspected principal lesion is not available for microscopic inspection

Histopathology in FCD Type IA



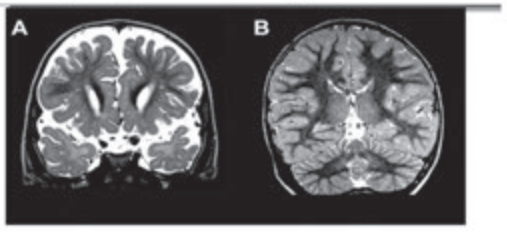
abnormal radial lamination and abundant microcolumns

Histopathological findings in FCD Type IB



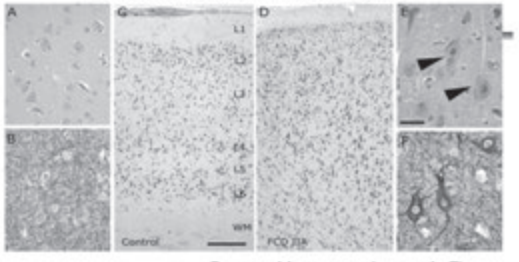
(abnormal tangential layer composition)

MRI findings in isolated FCD Type I



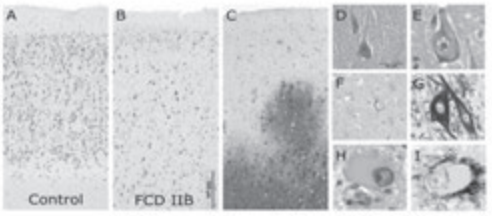
H. Holthausen and T. Piper

Histopathology in FCD Type IIA



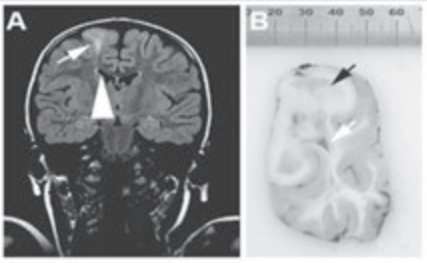
Dysmorphic neurons (arrows in E)

Histopathologiy in FCD Type IIB

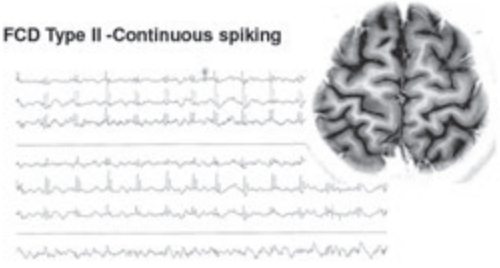


H: Balloon cells are a hallmark of this FCD variant

Neuroradiological-neuropathological correlation in FCD Type IIB

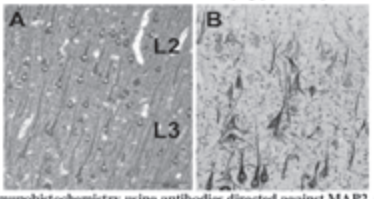


FCD Type II -Continuous spiking



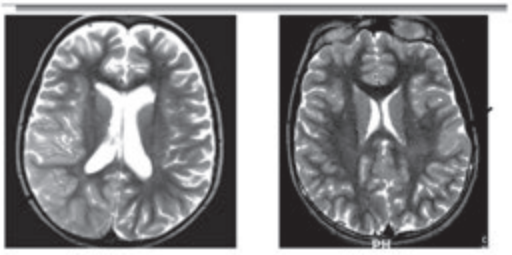
Cortesia Drs. Eliseu Paglioli Neto e André Palmini

FCD associated with MTS (Type IIIA)



- Immunohistochemistry using antibodies directed against MAP2. Cortical Layers 2 and 3 (L2, L3) cannot be separated as many neurons in L2 and L3 are hypertrophic. B: Immunohistochemistry using antibody SMI311. Intracytoplasmic accumulation of neurofilaments in hypertrophic neurons of Layer 2 and Layer 3. These abnormal neurons retain their pyramidal cell shape and apical dendrite. Scale bar in A = 100 µm.

Displasia cortical focal

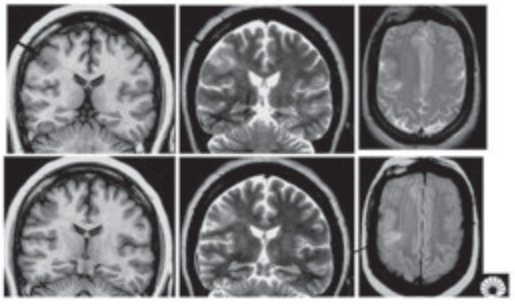


extensa localizada

Diagnóstico de displasia cortical focal em RM

- **Córtex espesso e/ou perda da nitidez da transição córtico-subcortical**
- **Geralmente acompanhada de:**
  - **Diferentes graus de anormalidade focal dos giros**
    - alteração na espessura, tamanho, forma, orientação dos giros e sulcos
  - **Aumento do sinal T2 e DP na substância branca adjacente**
  - **Sinal radial estendendo da área de córtex alterada em direção ao ventrículo (*transmantle sign*)**

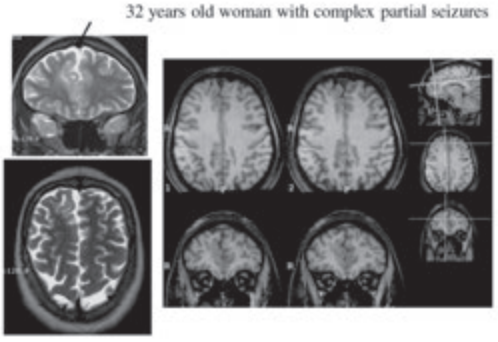
focal cortical dysplasia



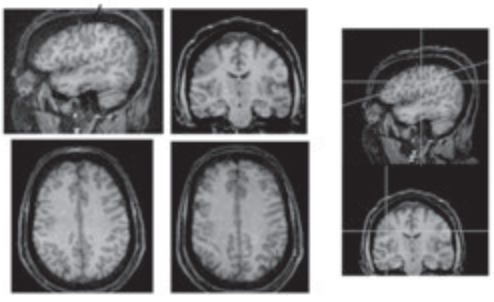
FCD and Epilepsy

- **Gradient of morphologic changes**
  - **from dysplastic lesions that can be easily identified by conventional MRI techniques**
  - **to minor structural abnormalities**
    - small areas of discrete cortical thickening and/or blurring of the gray-white matter interface
    - often go unrecognized

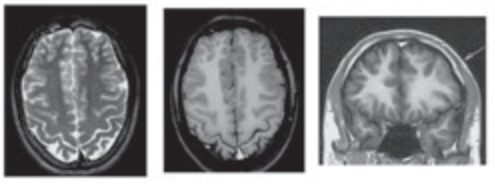
32 years old woman with complex partial seizures



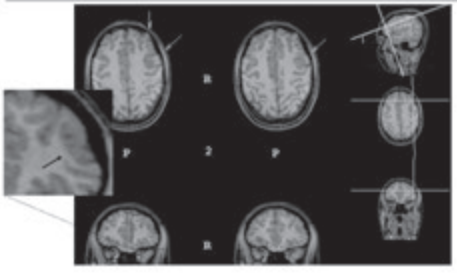
42 years old woman with partial seizures starting in the left side of the face



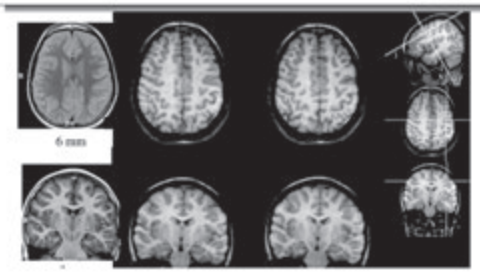
17 anos, crises de lobo frontal



MPR mostra lesão do tipo displasia cortical focal



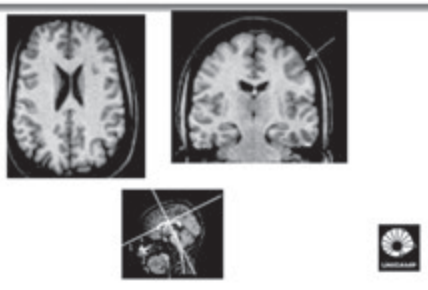
MPR:
menina de 7 anos com crises parciais motoras na mão direita



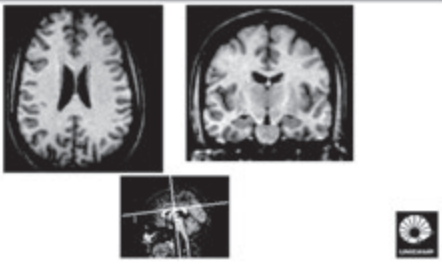
FCD and MPR

- The identification of these small FCD lesions by conventional MRI is often limited by the elaborate, contorted and irregular three-dimensional gyral structure
- The elaborate anatomy predisposes to the impression of cortical thickening due to obliquity of the plane of section in relation to the gyrus
- and volume averaging when using thick slices

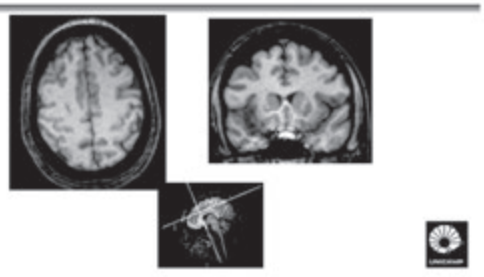
A) MPR: partial volume effect leading to false cortical thickening in a normal person



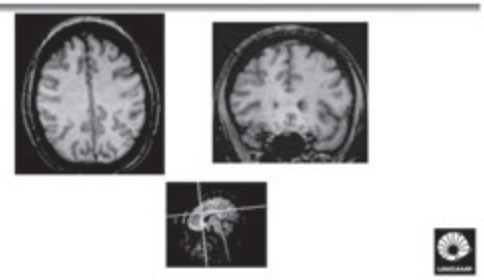
B) MPR: correction of partial volume effect by changing angulation

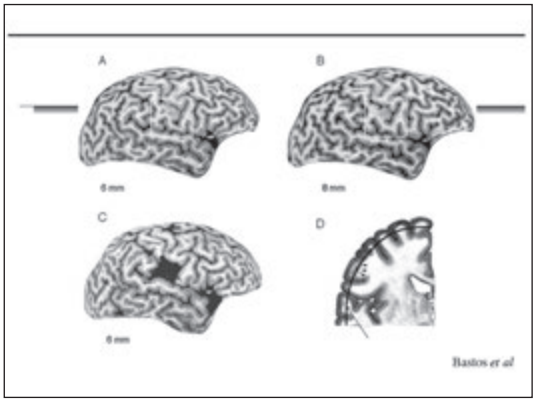


MPR: FCD in a patient with frontal lobe epilepsy



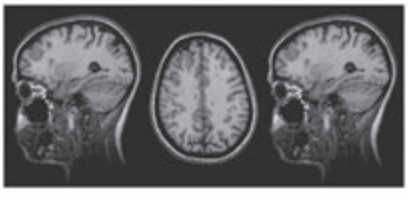
MPR: FCD in a patient with frontal lobe epilepsy
- no effect by changing angulation -





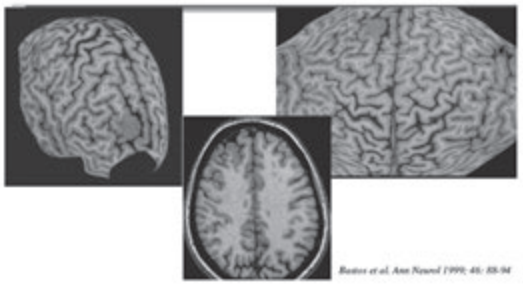
Curvilinear Reconstruction

Patient 1, FCD



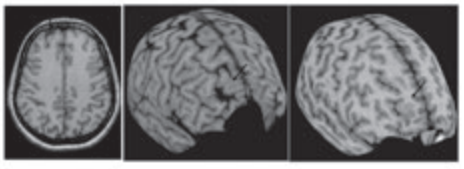
Bastos *et al*

Curvilinear reconstruction in cortical dysgenesis



Bastos et al. Ann Neurol 1999; 46: 88-94

focal cortical dysplasia

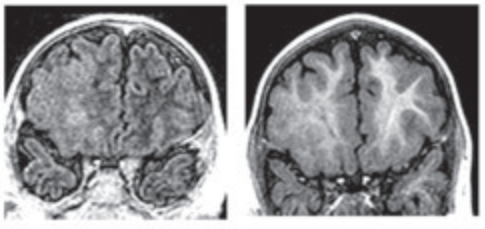


Bastos *et al*

Protocolos de RM nas Epilepsias extra-temporais

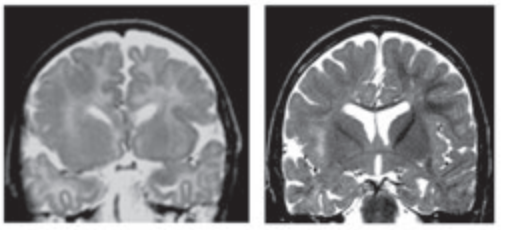
1. **Protocolo inicial para pacientes acima de 2 anos de idade:**
   - Coronal T1 (3mm ou menos)
   - Aquisição volumétrica de alta resolução (GRE) (<1.5mm)
   - Coronal T2 e FLAIR
   - Axial e Sagital T1
2. **Protocolo inicial para crianças abaixo de 2 anos de idade :**
   - Fast Spin Echo T2 e densidade de prótons
   - Aquisição volumétrica de alta resolução (GRE) (<1.5mm)
   - A RM pode não revelar alterações se a lesão for pequena e o exame de RM deve ser repetido

Myelination *versus* cortical dysplasia (T1-W)



3 meses 2 anos

Myelination *versus* cortical dysplasia (T2-W)



3 meses 2 anos

Distúrbios da migração neuronal

- **os neuroblastos migram aderidos (através de moléculas de adesão) às fibras radiais gliais da região periventricular até o córtex em formação**
  - **Período: 6ª a 7ª semanas até 20/24ª semanas**
    - pode persistir até período pós-natal

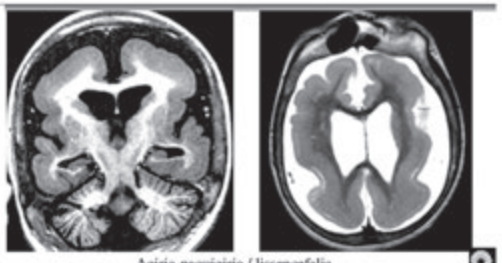
Distúrbios da migração neuronal

- **Agiria-paquigiria / lissencefalia**
  - **focal, multifocal, generalizada**
- **Heterotopias**
  - **nodular subcortical**
  - **subcortical "em bandas" ("córtex duplo")**
  - **nodular subependimária**

Normal cortex

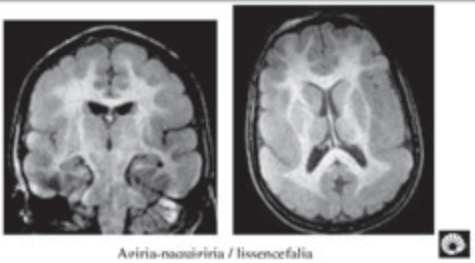
Classic lissencephalic cortex

N. 10 anos, sexo masculino, apresenta RDNPM grave, e epilepsia desde 5 meses de idade (Sd. Lennox-Gastaut)



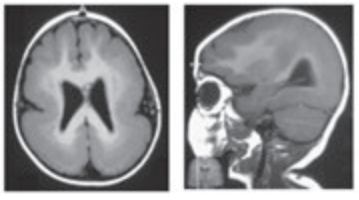
Agiria-paquigiria / lissencefalia

J., 3 anos, sexo masculino, apresenta RDNPM, hipotonia e visão subnormal - Epilepsia de difícil controle desde 4 meses de idade



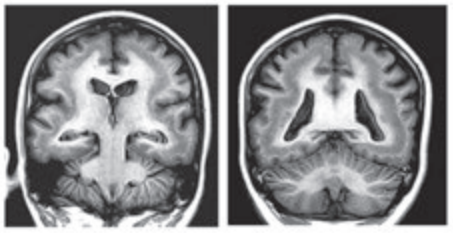
Agiria-paquigiria / lissencefalia

LIS1

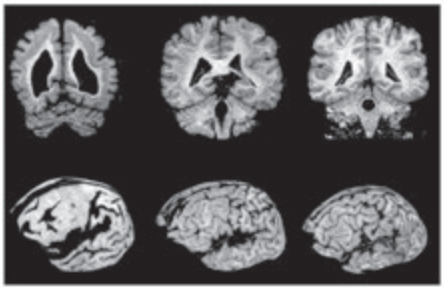


✓ grau 3a (agiria posterior - paquigiria anterior)

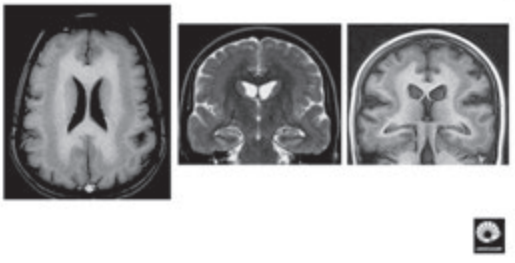
Heterotopia subcortical "em bandas" ("córtex duplo")



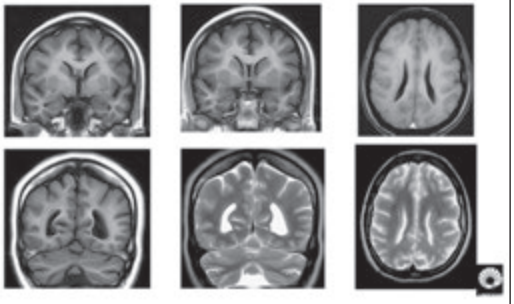
Heterotopia subcortical "em bandas" - *spectrum*



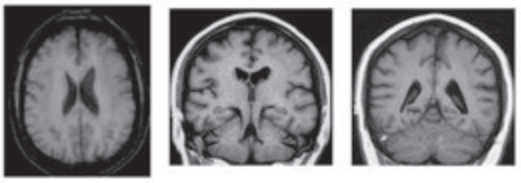
Heterotopia subcortical "em bandas" ("córtex duplo")



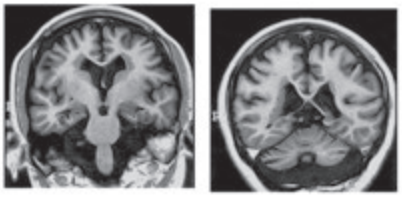
Heterotopia subcortical "em bandas"



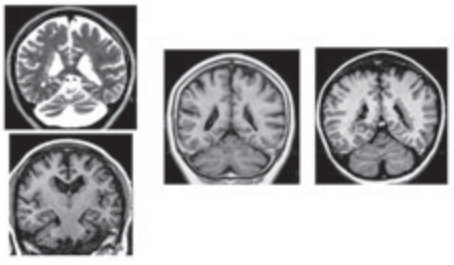
Subcortical laminar heterotopy, in a male patient
40 years old, secondary generalized epilepsy with focal features



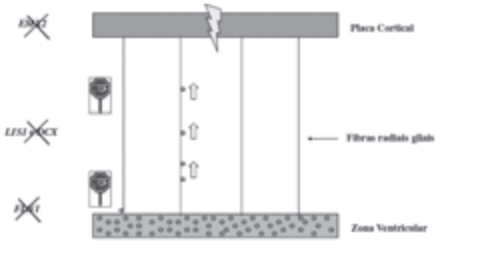
Heterotopia Nodular Periventricular



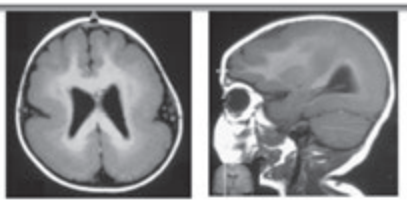
Heterotopia Nodular Periventricular



Distúrbios da migração e organização neuronal

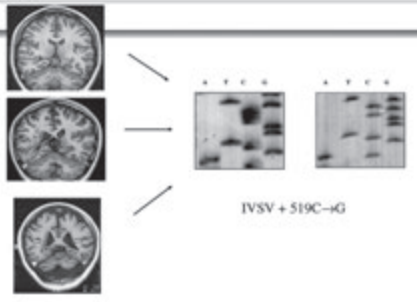


LIS1



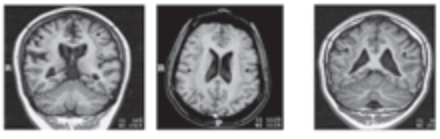
✓ grau 3a (agiria posterior - paquigiria anterior)

FLN1



DCX

Casos negativos - padrão típico



✓mosaicismo
✓ mutações nas regiões promotoras ou intrônicas
✓ grandes rearranjos
✓ outros genes

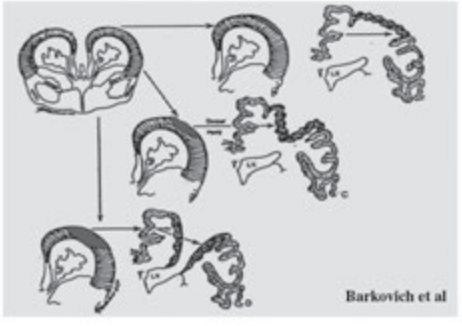
Distúrbios da organização cortical

Distúrbio do desenvolvimento cortical

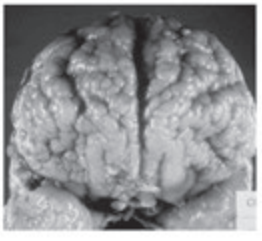
- Organização
- As primeiras células que chegam ao córtex (células de Cajal-Retzius) colocam-se na camada mais externa da lâmina cortical, determinando seu limite externo
- Em seguida chegam os neurônios que vão posicionar-se imediatamente abaixo da lâmina cortical (neurônios sub-laminares)
- Os neurônios que chegarem ao córtex vão se posicionar entre estes 2 limites, formando as 6 camadas
  - das mais profundas, para as mais superficiais (*inside-out*)

Distúrbios da organização cortical

- **Polimicrogiria**
- **Esquizencefalias**

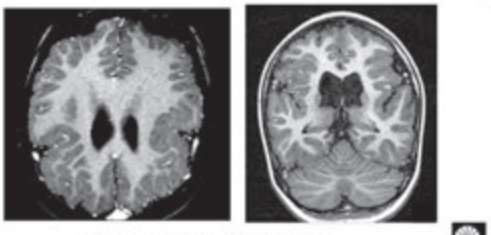


Polimicrogiria envolvendo os dois hemisférios



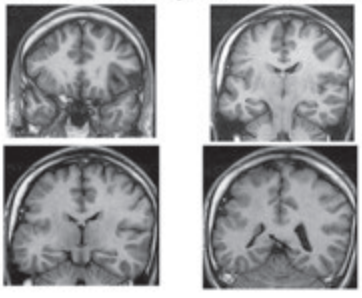
Polimicrogiria perisylviana

W., 11 anos, sexo masculino, apresenta dupla hemiparesia, quadro pseudo-bulbar e crises desde 4 meses de idade (Sd. Lennox-Gastaut)

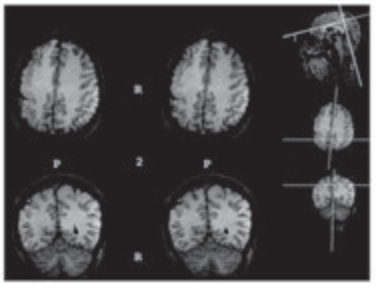


Polimicrogiria perisylviana bilateral

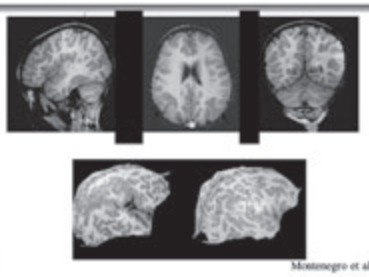
Polimicrogiria Perisylviana Unilateral
Associada a Heterotopia Nodular Periventricular



Polimicrogiria Perisylviana Unilateral

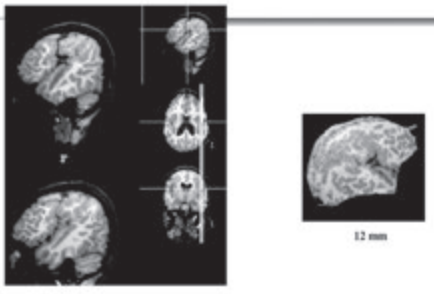


Bilateral Posterior Parietal Polymicrogyria: A Mild Form of Congenital Bilateral Perisylvian Syndrome?



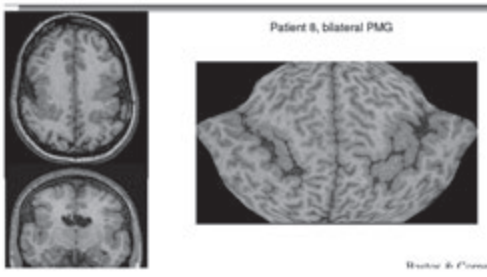
Montenegro et al; Epilepsia 2001

Polimicrogiria Perisylviana Bilateral



Polymicrogyria

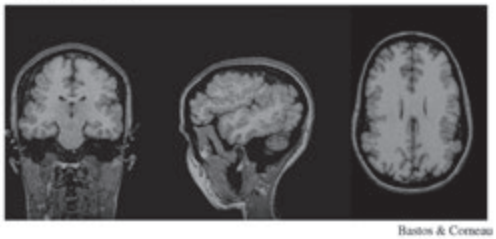
Patient 8, bilateral PMG



Bastos & Corneau

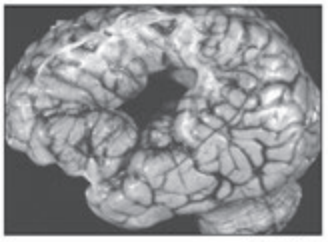
Polymicrogyria

Patient 9, bilateral PMG

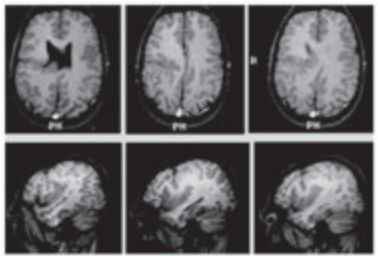


Bastos & Corneau

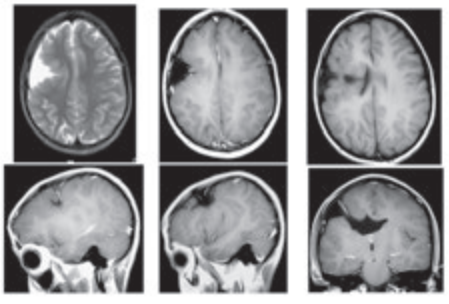
Esquizencefalia



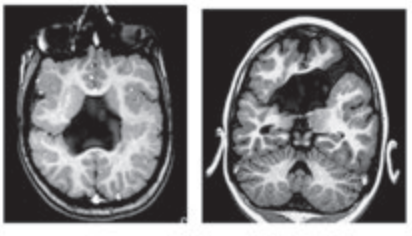
Esquizencefalia



Esquizencefalia

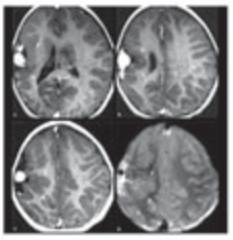


menina de 8 anos, apresenta RDNPM, microcefalia, dupla hemiparesia e epilepsia desde o período neonatal. Atualmente as crises estão controladas



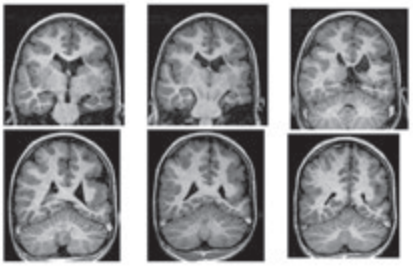
Esquizencefalia bilateral

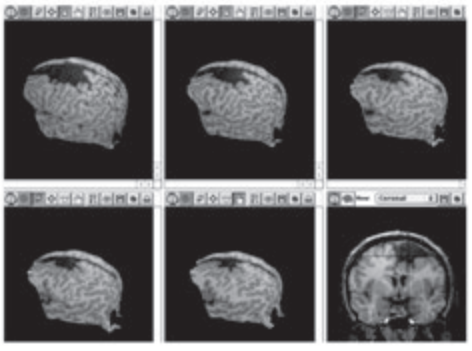
Polimicrogiria X Esquizencefalia (unilateral)



Polimicrogiria X Esquizencefalia

9 year old girl with seizures associated with cognitive and motor impairment





Conclusion - I

Abnormal Proliferation

- **More frequent and severe epilepsy**
  - **Functional and morphologically abnormal neurons**
  - **Intrinsic epileptogenicity**

Conclusion - II

Abnormal Migration

- **Frequency of epilepsy is lower than in FCD and higher than in polymicrogyria**
  - **Abnormal layering of neurons**
  - **Abnormal neuronal network ?**
    - Variable degrees of epileptogenicity

Conclusion - III

Abnormal Organization

- **Epilepsy is less frequent and more easily controlled**
  - **Abnormal layering of neurons**
  - **"Less" abnormal neuronal network ?**
    - Absent or mild intrinsic epileptogenicity

Maria Chiara Stefanini (Italy)

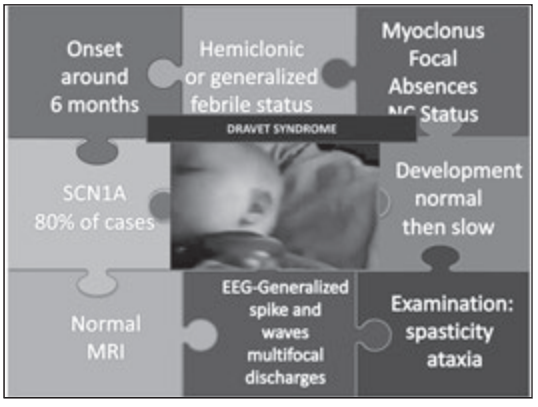
EPILEPSY IN AUTOIMMUNE ENCEPHALITIS

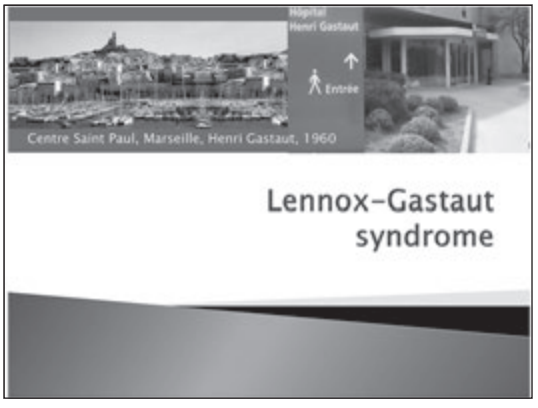
Carlo Alberto Tassinari (Italy)

ENCEPHALOPATHY RELATED TO STATUS EPILEPTICUS DURING SLEEP (ESES)

Elza Márcia Yacubian (Brazil)

DRAVET SYNDROME





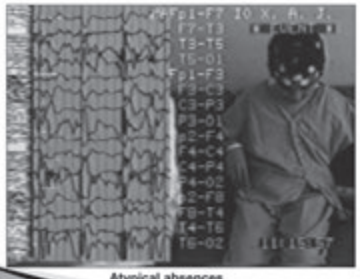
Lennox-Gastaut syndrome
Clinical aspects

- Onset between 1 and 7 years (peak 3-5 years);
- Cognitive and behavioural abnormalities (20-60% of patients);
- Boys more affected than girls (60%);
- Polymorphic seizures: atypical absences; tonic seizures; atonic seizures; myoclonic seizures (11-28% of cases);
- Neuropsychological deterioration.

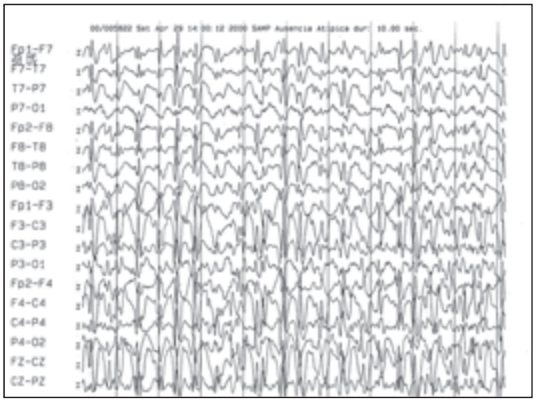
Charlotte Dravet's thesis in Marseille, 1966

Panayiotopoulos. The epilepsies: Seizures, syndromes and management 2005; 139-76

Lennox-Gastaut syndrome
Clinical aspects

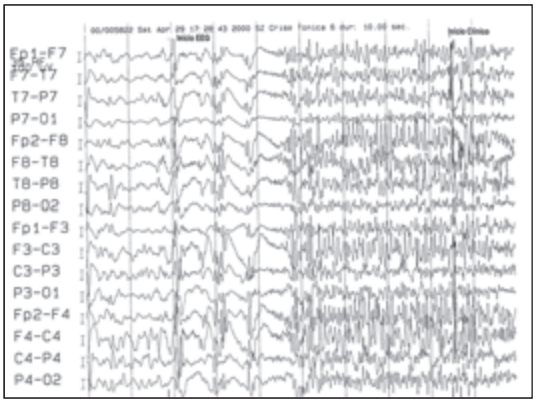


Atypical absences



Lennox-Gastaut syndrome
Clinical aspects

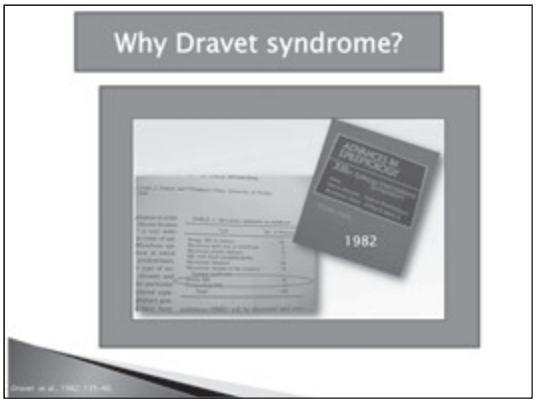
Tonic seizures



Dravet syndrome spectrum

Dravet syndrome
The history

Why Dravet syndrome?



Dravet syndrome
Clinical aspects

- 1978-1982- Centre Saint Paul- specific epileptic encephalopathy different of the Lennox-Gastaut syndrome;
- Onset before 1 year (peak 5 months) in normal children, without any relevant antecedent;
- Severe, prolonged convulsive seizures, first febrile, then afebrile.

Dravet syndrome
Clinical aspects

- Prolonged unilateral clonic seizures.

- Provoked by hyperthermia of around 38° C, temperature variations (body temperature unstable), minor infections, immunizations or hot baths

Dravet syndrome
Febrile seizures

- Prolonged beyond 15 or 30 minutes;
- Unilateral;
- Mainly clonic;
- Frequent;
- Precipitated by low fever often below 38° C;
- Vaccine controversy;
- Of early onset (before 1 year of age);
- Normal EEGs, normal development.

The diagnosis is nearly certain if intractable myoclonic jerks and mental deterioration appear within 1-2 years from onset

Dravet syndrome
Is early development really normal?

- Studies showing early on impaired visual function (tracking, visual attentiveness), prior to diagnosis, prior to seizure onset;
- Raises questions about the assumption that developemnt is always normal before onset of the epilepsy.

Dravet syndrome
Clinical aspects

- Afebrile seizures of mixed types including partial seizures;
- Development regression or stagnation;
- Normal neuroimaging.

Dravet syndrome
Clinical aspects

- Myoclonic seizures.

Dravet syndrome
Clinical aspects

- Atypical absences; obtundation status (40%).

Dravet syndrome
Clinical aspects

- Intractable seizures;
- Frequent and prolonged status epilepticus;
- Photosensitivity- eye closure, photic and pattern stimulation (1/4 self-induced seizures)-environment ligh intensity.

Epileptic encephalopathy without known etiology

Different of the Lennox-Gastaut syndrome

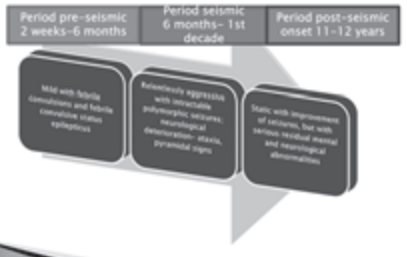
Severe myoclonic epilepsy in infants

Dravet syndrome
EEG

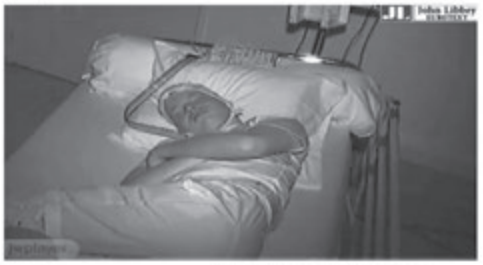
Dravet syndrome
Epidemiology

- Not well known;
- 1/40000 births (Hurt, 1990); 1/20 or 30000 births (Yakoub et al., 1992); less rare as genetic tests become available;
- Its frequency is probably higher;
- Males are more frequently affected than females (ratio of 2 to 1);
- Family antecedents of epilepsy and febrile convulsions (> 25%).

Dravet syndrome
Evolution- Three periods



Dravet syndrome
Clinical picture



- Convulsive seizures during sleep;
- Still precipitated by fever and infections

Dravet syndrome
Neuropathology

Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology

Brain 2011: 134; 2982–3010

Claudia B. Catarino, Joan Y.W. Liu, Ioannis Liagkouras, Vaneesha S. Gibbons, Robyn W. Labrum, Rachael Ellis, Cathy Woodward, Mary B. Davis, Shelagh J. Smith, J. Helen Cross, Richard E. Appleton, Simone C. Yendle, Jacinta M. McMahon, Susannah T. Bellows, Thomas S. Jacques, Sameer M. Zuberi, Matthias J. Koepp, Lillian Martinian, Ingrid E. Scheffer, Maria Thom and Sanjay M. Sisodiya

BRIEF COMMUNICATION

A case of SUDEP in a patient with Dravet syndrome with SCN1A mutation

François Le Gal, Christian M. Korff, Christine Monso-Hinard, Michael T. Mund, Michael Morris, Alain Malafosse, and Thomas Schmitt-Mechelke

- Micronodular dysplasia left temporal lobe
- Bilateral gliosis CA4
- Global cerebral edema

Dravet syndrome
Clinical picture

- In the 70's a very characteristic picture, many patients presenting with the same features;
- End of the 80's: patients with a less typical picture were reported– variability between the patients particularly for the myoclonic symptoms which was often very slight, even absent (1/5 patients). Tonic seizures, the hallmark of LGS, are exceptional.

Which were the borderlines of the syndrome?

2001– 80% cases SCN 1A mutations– it was an epileptic disease– 95% de novo; 5% familial; > 700 mutations described

Why Dravet spectrum?

Dravet spectrum

Febrile seizures – GEFS + – SMEB / ICE-GTCS / SIMFE – SMEI (Dravet syndrome)

MILD → SEVERE

DRAVET SYNDROME SPECTRUM– The borderline syndromes

• *SCN1A*-related seizure disorders (Dravet syndrome spectrum) includes the following syndromes, listed in order of increasing severity:

1. Familial Febrile Seizures (FS);
2. Generalized Epilepsy with Febrile Seizures Plus (GEFS+);
3. Intractable Childhood Epilepsy with Generalized Tonic-Clonic Seizures (ICE-GTC);
4. Severe Infantile Multifocal Epilepsy (SIMFE);
5. Severe Myoclonic Epilepsy Borderline (SMEB);
6. Severe Myoclonic Epilepsy of Infancy (SMEI); also called Dravet syndrome

DRAVET SYNDROME SPECTRUM– The borderline syndromes

• Generalized epilepsy with febrile seizures plus (GEFS+)

• Intermediate form of the spectrum;

• The seizures begin between infancy and 3 years old;

• Usually the first seizures are febrile seizures (up to 6 years old);

• After, afebrile seizures may persist after this age.

DRAVET SYNDROME SPECTRUM– The borderline syndromes

• Intractable Childhood Epilepsy with Generalized Tonic-Clonic Seizures (ICE-GTCS)

• More serious than GEPS +;

• 'Intractable' seizures distinguish it of GEFs +. Intractable means that are difficult to control with AEDs;

• Seizures are more frequent and more severe, the first occur before one year with fever;

• More generalized tonic-clonic seizures;

• No myoclonic seizures, no absences, what distinguishes ICE-GTC, of most severe form of the spectrum- Severe Myoclonic Epilepsy of Infancy (SMEI, Dravet syndrome).

DRAVET SYNDROME SPECTRUM– The borderline syndromes

• Severe Infantile Multifocal Epilepsy (SIMFE)

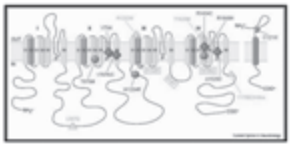
• Begins in the first year of life without other cause except febrile seizures;

• Multifocal seizures instead of typical generalized seizures of the Dravet spectrum;

• Children with SIMFE present simple and complex partial seizures;

• Children with SIMFE do not present myoclonic seizures and absences.

Dravet syndrome
Clinical picture



- Is this a single disease with different forms related to different mutation types?
- Is this disease a part of a large spectrum of channelopathies including other myoclonic and non-myoclonic epilepsies?

Am. J. Hum. Genet. 68:1327–1332, 2001

De Novo Mutations in the Sodium-Channel Gene *SCN1A* Cause Severe Myoclonic Epilepsy of Infancy

Lieve Claes,[1] Jurgen Del-Favero,[1] Borten Ceulemans,[1,2] Lieven Lagae,[3,4] Christine Van Broeckhoven,[1] and Peter De Jonghe[1,2]

- In 3% of cases of Dravet syndrome, other genes, including *GABRG2* and *PCDH19 (when SCN1A is negative in a girl);*
- Approximately 17% of patients with a clinical diagnosis of Dravet syndrome have an unspecified genetic mutation.

Regardless the type of mutation the syndrome is the same!

Dravet syndrome
Mechanisms

- Animal model: reduced sodium channel currents in GABAergic inhibitory interneurons but not in the excitatory pyramidal neurons;

Dravet syndrome
Treatment

The diagnosis is clinical- early diagnosis can be made by molecular approach

Algorithms

1. Valproato(Depakote, Depakene)- even if the seizure had a focal component)
2. Clobazam (Frisium, Urbanil) (avoided in Germany)
3. Stiripentol (Diacomit)*- orphan drug- 2 RCT
4. Bromides (Germany, Japan)
5. Topiramato (Topamax)
6. Levetiracetam (Keppra)
7. Other benzodiazepines

Dravet syndrome
Treatment

The diagnosis is clinical- early diagnosis can be made by molecular approach

Algorithms

1. **Myoclonic seizures**
   - Valproate, benzodiazepines, levetiracetam
2. **Absences**
   - Valproate, benzodiazepines, ethosuximide
3. **Partial seizures**
   - Same treatment as for GTC seizures

Dravet syndrome
Aggravation

- ❑ – Carbamazepina (Tegretol)
- ❑ – Fenitoína (Hidantal)
- ❑ – Lamotrigina (Lamictal)
- ❑ – Oxcarbazepina (Trileptal)
- ❑ – Vigabatrina (Sabril)

Dravet syndrome
Non DrugTreatment

- ❑Ketogenic diet
- ❑Stimulation of vagus nerve

Dravet syndrome
Rescue medication

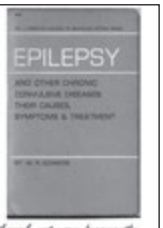
- ❑ Prolonged seizures or status epilepticus:
  - Early treatment of infectious diseases and hyperthermia, which are their triggering factors;
  - Benzodiazepines.

Dravet syndrome
Adjunctive treatment

- Photosensitivity
  - Sunglasses
  - Avoid light stimulation (videogames, TV)
- Prevention of accidents related to seizures
  - Bath, swimming pools, falls, agitation, etc
- Educational treatment and training measures

Treatment

WILLIAM GOWERS
(1845–1915)



...Cannabis indica is sometimes, though not very frequently, useful. It is of small value as an adjunct to bromide, but is sometimes of considerable service given separately ... It is also capable of causing delirium and sleep, first depression and then acceleration of the heart, and also dilates the pupil... The cerebral excitement is relatively more marked than in the case of belladonna...

Epilepsy and Other Chronic Convulsive Diseases: their Causes, Symptoms & Treatment, 1881 pp. 223-4

Cannabinoids– Medical marijuana

Gloss D, Vickrey B. *Cochrane Database of Systematic Reviews*. 2012; Issue 6.

Desperate parents turn to medical marijuana in last-ditch effort to improve their children's lives

- More specifically a specific component of marijuana known as cannabidiol (CBD). This component of the marijuana plant does not produce the psychoactivity that tetrahydrocannabinol (THC) does;
- Medical marijuana– High in CBD but low in THC.

Orrin Devinsky

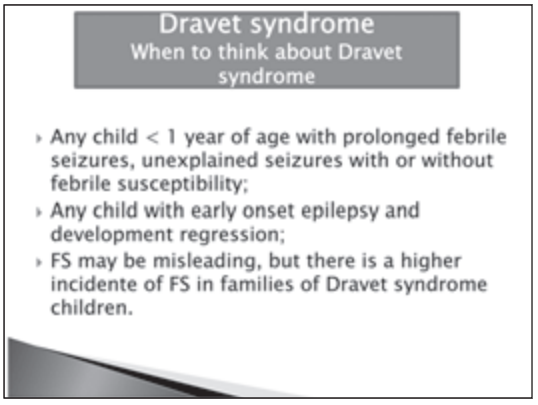
Brief Communication

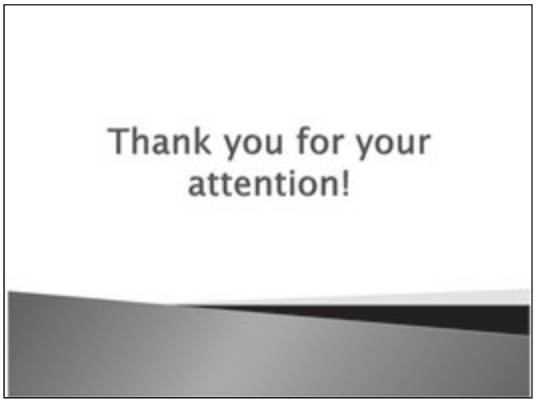
Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter, Catherine Jacobson *

Epilepsy & Behavior 29 (2013) 574–577

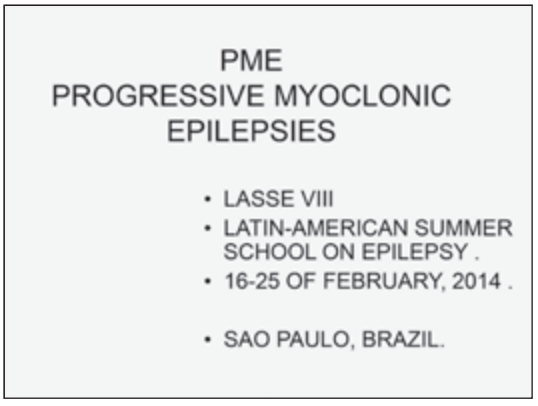
Orrin Devinsky MD, Director of the Comprehensive Epilepsy Center at New York University, was recently awarded FDA approval to conduct a clinical trial that will study the safety and tolerability of cannabidiol (CBD) in children with epilepsy.

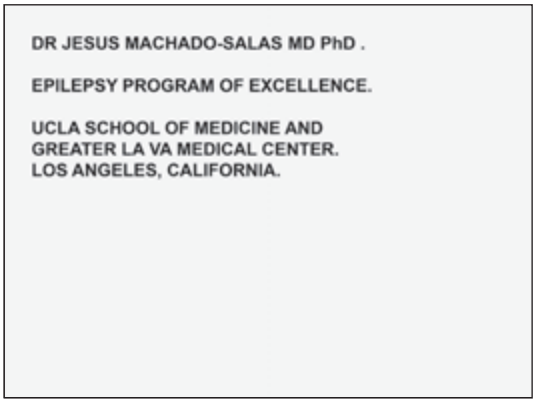

Dravet syndrome
When to think about Dravet syndrome
Any child < 1 year of age with prolonged febrile seizures, unexplained seizures with or without febrile susceptibility;
Any child with early onset epilepsy and development regression;
FS may be misleading, but there is a higher incidente of FS in families of Dravet syndrome children.

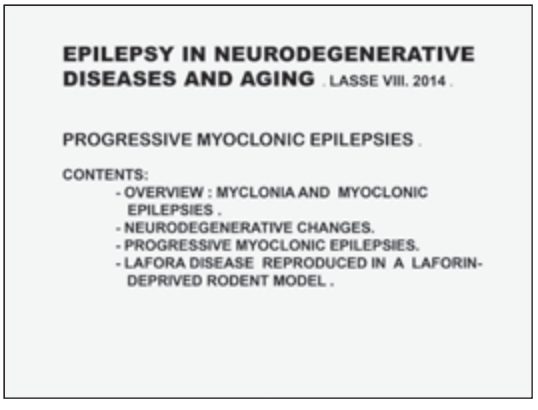

Thank you for your attention!

Jesus Machado Salas (USA)

PME







PROGRESSIVE **MYOCLONIC** EPILEPSIES .

HISTORY .

UNVERRICHT 1891.....DIE **MYOKLONIE** .
First description of a FAMILIAL EPILEPSY DISEASE and
First time use of the word MYOCLONUS .

LUNDBORG 1903.....DIE PROGRESSIVE **MYOKLONUS**-EPILEPSIE.
A ten families full description of this RARE form of Epilepsy .

LAFORA AND GLUECK 1911.....LAFORA DISEASE . PAS + .

RAMSAY HUNT 1921.....DYSSINERGIA CEREBELLARIS **MYOCLONICA**.

FATAL FORM OF MYOCLONIC EPILEPSIES .

HERP IN 1857.....EPILEPTIC SECOUSSES .

RABOT 1899.....LA **MYOCLONIE** EPILEPTIQUE . (MD THESIS)

JANZ AND CHRISTIAN 1957.....IMPULSIV PETIT MAL
(OCCURRENCE OF MINOR SEIZURES WITH FORWARD-DIRECTED JERKS)

CASTELLS AND MENDILAHARSU (URUGUAY) 1958)
BILATERAL **MYOCLONIC** AND CONSCIOUS EPILEPSY .

GASTAUT 1952..... MASSIVE BILATERAL **MYOCLONIC** JERKS OF ADOLESCENCE.

NON-FATAL FORM OF MYOCLONIC EPILEPSY

DOOSE 1964.....DAS AKINETISCHE PETIT MAL.
MYOCLONIC ASTATIC EPILEPSY (DROP ATTACKS: A SUDDEN COMBINATION OF A MASSIVE JERK AND AN ABSOLUTE AND BRISK ATONIA) .

TASSINARI 1969. 1985 ..... EPILEPSY WITH **MYOCLONIC** ABSENCES, (CAE WITH UPPER LIMBS MYOCLONIAS); POOR PROGNOSIS, DRUG-RESISTANCE AND MENTAL DETERIORATION.

JEAVONS SYNDROME 1977...EYELID MYOCLONIAS WITH ABSENCES.

PANAYIOTOPOULOS 1994.....ABSENCES WITH PERIORAL **MYOCLONIAS** .

MYOCLONIC EPILEPSY / EPILEPSIES .

PLURALITY AND COMPLEXITY OF THE FIELD .

EPILEPSY ENTITIES DISPLAYING **MYOCLONIAS**:
(ILAE INT CLASSF, 1989)
- **IDIOPATHIC FOCAL EPILEPSIES**:
BENIGN ROLANDIC EPILEPSIES (NEGATIVE MYOCLONUS)
PRIMARYREADING EPILEPSY
- **SYMPTOMATIC FOCAL EPILEPSIES**:
EPILEPSIA PARTIAL CONTINUA (TYPE I Y II).
- **IDIOPATHIC GENERALIZED EPILEPSIES (GENETIC)**
BENIGN MYOCLONIC EPILEPSY IN INFANCY.
JUVENILE MYOCLONIC EPILEPSY.
OTHER LIKE IDIOPATHIC GE WITH PHOTOSENSITIVITY.
- **SYMPTOMATIC OR CRYPTOGENIC GENERALIZED EPILEPSIES**:
MYOCLONIC-ASTATIC EPILEPSY (DOOSE SYNDROME)
LENNOX-GASTAUT SYNDROME (MYOCLONIC FORM)
EPILEPSY WITH MYOCLONIC ABSENCES
- **EPILEPSIESUNDETERMINED WHETHER GENERALIZED OR FOCAL**
DRAVET SYNDROME: SEVERE MYOCLONIC EPILEPSY IN INFANCY

MYOCLONIC EPILEPSY / EPILEPSIES .

PLURALITY AND COMPLEXITY OF THE FIELD 2 .

EPILEPSY ENTITIES DISPLAYING MYOCLONIAS. : (TASK FORCE 2001) **ACHT CHECK THIS !!!!**

LIST OF SYDROMES:

BENIGN MYOCLONIC EPILEPSY IN INFANCY.
DRAVET'S SYNDROME (SME INFANCY)
EPILEPSY WITH MYOCLONIC ABSENCES
EPILEPSY WITH MYOCLONIC-ASTATIC SEIZURES
LENNOX-GASTAUT SYNDROME
PROGRESSIVE MYOCLONUS EPILEPSIES
IGE WITH VARIABLES PHENOTYPES, INCLUDING JME.
REFLEX EPILEPSIES, PRIMARY READING EPILEPSY

MYOCLONIC STATUS IN NONPROGRESSIVE ENCEPHALOPATHIES.
GENERALIZED EPILEPSIES WITH FEBRILE SEIZURES PLUS.

YA INCORPORADOS ?????????????? TASK FORCE RECIENTE .

MYOCLONUS: DEFINITION. TYPES. MECHANISMS. CLINICAL RELEVANCE.

A BRIEF, MODERATE TO INTENSE INVOLUNTARY MOVEMENT OCCURRING IN A BODY SEGMENT OR THE WHOLE BODYWITHOUT APPARENT CAUSE.

MYOCLONUS CAN BE POSITIVE OR NEGATIVE (MUSCLE ACTIVATION OR LACK OF ACTIVATION) (EMG) .

LUNDBORG (1903) : TYPES:
SYMPTOMATIC MYOCLONUS, **ESSENTIAL** MYOCLONUS, AND **FAMILIAL** MYOCLONIC EPILEPSY (PROGRESSIVE AND NON-PROGRESSIVE).

MUSKENS (1928) CREATES THE TERM "FRAGMENTS OF EPILEPSY" TO DESIGNATE MYOCLONUS IN EPILEPTIC PATIENTS.

EPILEPTIC MYOCLONUS: CLINICAL FEATURES:

- POSITIVE OR NEGATIVE .
- FOCAL . MULTIFOCAL . GENERALIZED .
- SPONTANEOUS. REFLEX (INDUCED BY MOVEMENT , SENSORY OR VISUAL STIMULI .
- RHYTMIC OR ARRHYTMIC .

- BASIC NEUROPHYSIOLOGY:
- DURATION 10 TO 100 MILLISECONDS (POSITIVE **M**) .
- DURATION OF SILENT PERIOD : 50 TO 400 MSEC (NEGATIVE **M**) .
- PRESENCE OF A TIME-LOCKED EEG CORRELATE IN CORTICAL **M** .

- CORTICAL MYOCLONUS ORIGINATE FROM ABNORMAL NEURONAL DISCHARGES IN THE SENSORIMOTOR CORTEX. OCCIPITAL AND/OR PARIETAL CORTICES MAY PARTICIPATE AS THE EXCITATION SOURCE.

- IN CORTICAL MYOCLONUS, RHYTMIC CORTICAL GENERATORS ARE OBSERVED IN IV AND V CORTICAL LAYERS .

MYOCLONUS (M) : ETIOLOGICAL CLASSIFICATION .

1) PHYSIOLOGIC **M**. : SLEEP, HICCUP, AND INDUCED BY ANXIETY OR EXERCISE .

2) ESSENTIAL **M**. : JUST **M**. NO OTHER NEUROLOGIC SIGNS.

3) EPILEPTIC **M**. : **M**. IN EPILEPTIC PATIENTS.

4) SYMPTOMATIC **M**. : **M**. IN ENCEPHALOPATHY.

EPILEPTIC MYOCLONUS : OCCURS IN EPILEPSY AND IT RELATES TO A CORTICAL SPIKE. SOME AUTHORS CONSIDER ALSO A POTENTIAL SUBCORTICAL ORIGIN FOR THE SPIKE AND RELATED MYOCLONUS.

EPILEPTIC M. TYPES:
- POSITIVE AND NEGATIVE CORTICAL MYOCLONUS . (DESCENDING VOLLEY)
- THALAMOCORTICAL MYOCLONUS . (ASCENDING VOLLEY/DESCENDING VOLLEY)
- RETICULAR MYOCLONUS . (LOW B-S ASCENDING VOLLEY : XI----VII----V)

NEURODEGENERATION .

NEURODEGENERATIVE CHANGES .

NEURODEGENERATIVE DISEASES .

NEURODEGENERATION / NEURODEGENERATIVE CHANGES 1 :
THE BASICS .
FROM CAJAL TO AN EXPERIMENTAL MODEL OF LAFORA DISEASE .

THE AGING BRAIN SHOWS MANY MACROSCOPIC CHANGES.
ALSO, IT DISPLAYS SOME MICROSCOPIC AND ULTRAMICROSCOPIC CELLULAR CHANGES THAT ARE CONSIDERED NORMAL FOR OLD AGE.

SENILE TRIAD:
SENILE PLAQUES .
NEUROFIBRILLARY CHANGES ,
GRANULOVACUOLAR DEGENERATION .

BLOCQ AND MARINESCO , 1892 : "SUR LES LESIONS ET LA PATHOGENIE DE L-EPILEPSIE DITE ESENTIELLE ." THEY MADE THE FIRST DESCRIPTION OF SOME SMALL NODES PRESENT ALL OVER THE CEREBRAL CORTEX OF A SENILE EPILEPTIC PATIENT.THE SENILE PLAQUES.

IN 1911, **SIMCHOWICZ** NAMED THESE SMALL NODULES AS **SENILE PLAQUES** . IN THE SAME YEAR **BIELSCHOWSKI** PUBLISHED A DETAILED DESCRIPTION OF SENILE PLAQUES .

NEURODEGENERATION/NEURODEGENERATIVE CHANGES 2

FOR MORE THAN A CENTURY IT HAS BEEN KNOWN THAT **SENILE PLAQUES** CONTAIN DEGENERATED NEURITES, MICROGLIAL AND ASTROCYTIC PROLONGATIONS AND A CENTRAL CORE OF AMYLOID .

MANY STUDIES MADE IN THE LAST 4 OR 5 DECADES HAVE SHOWN A CLOSE CORRELATION BETWEEN THE NUMBER OF **SENILE PLAQUES** AND THE LEVEL OF INTELLECTUAL DETERIORATION IN OLD AGE. AFTER THESE STUDIES, IT BECAME EVIDENT A CLOSE DIRECT CORRELATION BETWEEN THE NUMBER OF **SENILE PLAQUES** AND DEGREE OF DEMENTIA.

SENILE PLAQUES ARE ARGYROPHILIC AND STRONGLY REACT TO **PAS** STAIN.
THEY CAN BE SEEN IN THE BRAIN OF DOWN'S SYNDROME PATIENTS, AS WELL AS IN THE CNS OF OLD INDIVIDUALS FROM MANY SPECIES.

IN HUMANS, THEY ARE SELDOM SEEN IN THE CEREBELLUM.

NEURODEGENARATION/ NEURODEGENERATIVE CHANGES 3

ALOIS ALZHEIMER DESCRIBED THE **NEUROFIBRILLARY CHANGES** OBSERVED IN A 51-YEAR-OLD DEMENTED WOMAN. HER NEUROLOGIC DETERIORATION STARTED FIVE YEARS BEFORE. IT WAS THE FIRST SCIENTIFIC DESCRIPTION THAT CORRELATED **NF** CHANGES TO PRE-SENILE DEMENTIA. (AGING AND SENILE DEMENTIA) .

THE SKELETON OF NERVE CELLS WAS WELL KNOW TO CLASSIC NEUROHISTOLOGISTS FROM THE TRANSITION OF THE XIX TO THE XX CENTURY.
REMAK, LEYDIG,KUPFFE AND SPECIALLY THE EXTRAORDINARY SPANIARD **DON SANTIAGO RAMON Y CAJAL**, DID REMARKABLE OBSERVATIONS .
THEY DEMONSTRATED THE PRESENCE OF NEUROFIBRILS (NEUROFILAMENTS) IN NORMAL NERVE CELL SOMATA AND NEURITES. MULTIPLE ILLUSTRATIONS, DRAWN BY CAJAL'S HAND, CAN BE STUDIED IN HIS MARVELOUS BOOK: **"LA HISTOLOGIE DU SYSTEME NERVEUX DE L'HOMME ET DES VERTEBRES".**
ALSO, HE OBSERVED CHANGES IN THE NEUROCYTOSKELETON INDUCED BY TEMPERATURE, INFECTION OR RABIES.

A WORD ON THE NEUROCYOSKELETON .

MICROTUBULES 20 NANOMETERS DIAMETER .
SOMA>>>>NEURITES AND
NEURITES >>>>> SOMA TRANSPORTATION .
(ORGANELLES AND MOLECULES) .

INTERMEDIATE FILS (NF) 10 NANOMETERS DIAMETER . SHAPE, MOVEMENT AND GROWTH OF SOMATA , NEURITES, INCLUDING GROWING NEURITES AND SYNAPTIC BOUTOUNS .
A MOBILE SKELETON .

MICROFILAMENTS 5 NANOMETERS DIAMETER .
INTRACYTOPLASMIC SUBMEMBRANE FILAMENTOUS PROTEINS, VERY DYNAMIC : ACTIN .

NEURODEGENERATION/ NEURODEGENERATIVE CHANGES 3

NEUROFIBRILLARY CHANGES, AS SEEN WITH THE LIGHT MICROSCOPE, APPEAR AS DARK, THICK BANDS THAT OCCUPY A LARGE PORTION OF THE NEUROCYTOPLASM AND DENDRITES. THEY ARE NOT PRESENT IN AXONS.

THE THIN, SMOOTH PROFILES OF NEUROFILAMENTS (NEUROFIBRILS) HAS BEEN SUBSTITUTED BY THIS GROSS ACCUMULATION OF DEGENERATED CYTOSKELETON ELEMENTS . THEIR PRESENCE AND RELEVANCE IN DEMENTIA CASES IS KNOWN SINCE DR. ALZHEIMER OBSERVATIONS (1906, 1911) (KRAEPELIN).

DURING THE SECOND HALF OT THE XXTH CENTURY, WE LEARNED THAT **NEUROFIBRILLARY CHANGES** OCCUR IN DIFFERENT NEUROLOGIC DISEASES .

NEURODEGENERATION/ NEURODEGENERATIVE CHANGES 4

THE LAST ELEMENT OF THE SENILE TRIAD , AS SEEN WITH THE LIGHT-MICROSCOPE, IS THE SO CALLED GRANOVACUOLAR DEGENERATION. ALSO DESCRIBED BY SIMCHOWICZ IN CASES OF SENILE DEMENTIA.

THEY ARE 5 MICRON DIAMETER CLEAR VACUOLES, CONTAINING AN ARGYROPHILIC GRANULE. THIS GRANULE IS PAS-NEGATIVE AND IT SHOWS NO AFFINITY FOR CONGO RED. IT IS MAINLY SEEN IN THE HIPPOCAMPUS FROM DEMENTED OR ELDERLY PERSONS.

NEURODEGENERATION . NEURODEGENERATIVE CHANGES .
NEURODEGENERATIVE DISEASES .
A MOLECULAR OVERVIEW .

NDG DISEASES: MANY ! , AND ALL OF THEM HAVE EMERGED THANKS TO MOLECULAR BIOLOGY STUDIES AND ANATOMOCLINICAL CORRELATION. JUST A FEW EXAMPLES :

TAUOPATHIES ARE NEURODEGENERATIVE DISEASES CHARACTERIZED BY THE INTRANEURONAL AGGREGATION OF MICROTUBULE-BINDING TAU PROTEIN.

TAU IS A MAP OR MBP. ITS APARENT FUNCTION IS TO MAINTAIN THE PROPER DISTANCE AND PARALELLISM AMONG MICROTUBULES . UNDER NORMAL CONDITIONS TAU IS MAINLY PRESENT IN AXONS .

NEUROFIBRILLARYY CHANGES : AN ACCUMULATION AND AGGREGATION OF HYPERPHOSPHORYLATED MICROTUBULE ASSOCIATED TAU PROTEINS, FORMING INSOLUBLE NEUROFIBRILLARY TANGLES. (PAIRED HELICAL FILAMENTS)

TAUOPATHIES 2

THERE ARE MORE THAN 30 TAUOPATHIES. AUTOSOMAL DOMINANT MUTATIONS HAVE BEEN FOUND IN THE MAPTAU GENE (CHROM 17) OF PATIENTS WITH FT DEMENTIA, A TAUOPATHY.

(AD, CORTICOBASAL DEGENERATION, PROGRESSIVE SUPRANUCLEAR PALSY AND PICK'S DISEASE, ETC.)

ANOTHER EXAMPLE OF "MOLECULAR DISEASES":

SPLICEOPATHY : FAILURE IN SPLICING .
SPLICING: TO CUT AND JOIN FRAGMENTS OF GENETIC MATERIAL DURING TRANSCRIPTION.

EVEN THOUGH ALL TAUOPATHIES SHOW INTRANEURONAL TAU AGGREGATES, THEIR CLINICAL SYMPTOMS AND HISTOPATHOLGICAL APPEARENCE DIFFER. FOR EXAMPLE: PAIRED HELICAL FILAMENTS, STRAIGHT FILAMENTS OR PICK BODIES. ALSO THE NEURONAL AND GLIAL INVOLVEMENT IS NOT ALWAYS THE SAME AMONG DISEASES . HOWEVER, A PROMINENT GLIOSIS IS ALWAYS OBSERVED .

IN THE HUMAN ADULT BRAIN THERE ARE SIX ISOFORMS OF TAU PROTEIN . ALL OF THEM ARE AGGREGATED IN AD, WHEREAS IN PICK'S DISEASE AND PROGRESSIVE SUPRANUCLEAR PALSY ONLY TWO ISOFORMS ARE INVOLVED.

LEWY BODIES, ANOTHER TYPE OF NEURODEGENERATIVE NEURONAL INCLUSIONS, ARE MAINLY COMPOSED OF ALFA-SINUCLEIN AND ARE CHARACTERISTIC OF PKD AND DEM-LB .

MARINESCO BODIES ARE PRESENT IN NUCLEI OF PIGMENTED NEURONS. LIKE SUBSTANTIA NIGRA AND LOCUS COERULEUS. THEY IMMUNOREACT TO UBIQUITIN . RECENTLY IT WAS FOUND THAT THE NUMBER O MARINESCO BODIES KEEP AN INVERSE RELATION WITH THE INTEGRITY OF THE DOPAMINERGIC SYSTEM .

THE **GRANULOVACUOLAR DEGENERATION** IS A COMPLEX MOLECULAR MIXTURE. IT IMMUNOREACT TO: A LATE-STAGE AUTOPHAGIC MARKER (Lamp-1) , AND THE CENTRAL GRANULE CONTAINS AN ENDOSOMAL SORTING COMPLEX, CHARGED MULTIVESICULA BODY PROTEIN 2B, UBIQUITIN AND PHOPHO-TDP-43 .

GVD IS MORE FREQUENTLY SEEN IN AD. IT HAS ALSO BEEN REPORTED IN PICK'S D, PROG SUPNUCK PALSY AND CXBA-D .

PICK'S BODY IS NEGATIVE TO ALFA-SYNUCLEIN AND POSITIVE TO TAU PROTEIN , PHOSPHORYLATED NEUROFILAMENT PROTEIN AND UBIQUITIN.

PROGRESSIVE MYOCLONUS EPILEPSIES .

PROGRESIVE MYOCLONUS EPILEPSIES .

IT IS A MIXED GROUP OF EPILEPSIES SHARING AN AUTOSOMAL RECESSIVE WAY OF INHERITANCE.

- LAFORA DISEASE
- UNVERRICHT-LUNDBORG DISEASE
- NEURONAL CEROID LIPOFUSCINOSIS
- TYPE I SIALIDOSIS (CHERRY-RED SPOT MYOCLONUS)
- ACTION MYOCLONUS-RENAL FAILURE SYNDROME
- TYPE III GAUCHER'S DISEASE.

- WHEN AFFECTED BY ANY OF THESE DISEASES , NORMALLY APPEARING CHILDREN SHOW A COGNITIVE REGRESION, SOME SORT OF NEUROLOGICAL IMPAIRMENT, DEMENTIA , **MYOCLONUS** AND VARIOUS FORMS OF EPILEPSY. EARLY DEATH IS USUALLY EXPECTED.

PME 2
ESSENTIALS:

- NEUROPATHOLOGICAL CHANGES MAINLY INVOLVE GRAY MATTER.
- THESE CHANGES AFFECT MOST ENCEPHALIC NUCLEI, INCLUDING CEREBELLAR CORTEX AND DEEP NUCLEI.
- EVEN THOUGH THE INVOLVED GENES VARY FROM ONE DISEASE TO ANOTHER, IN ALL OF THEM THERE IS ALWAYS AN AUTOSOMAL RECESSIVE MECHANISM.

- **LYSOSOMAL** INVOLVEMENT (OR NOT) DETERMINES TWO MAJOR SUBGROUPS:
- NON-LYSOSOME-RELATED DISEASE: **LAFORA DISEASE**, AND
- LYSOSOME-RELATED DISEASES: UNVERRICHT-LUNDBORG DISEASES, THE ACTION-MYOCLONUS-RENAL FAILURE SYNDROME AND NEURONAL CEROID LIPOFUSCINOSIS, SIALIDOSIS AND GAUCHER'S DISEASE.

PME 3

ALSO, THERE IS ONE FORM OF PME WHICH INVOLVES AN AUTOSOMAL DOMINANT MECHANISM: DENTATORUBROPALLIDOLUYSAN ATROPHY.

FINALLY, AN EQUALLY AGGRESSIVE FORM OF PME IS ASSOCIATED TO MITOCHONDRIAPATHIA: MYOCLONIC EPILEPSY WITH RAGGED-RED FIBERS.

PME 5
AN OVERVIEW OF PMEs ;
UNVERRICHT-LUNDBORG DISEASE.

- IT APPEARS AROUND 6 TO 13 YEARS OF AGE
- DOMINANT SIGNS: MYOCLONUS AND ATAX IA . THESE SIGNS BECOME WORST DURING ADOLESCENCE.
- DURING ADULTHOOD, ULD BECOMES STABLE AND SYMPTOMATOLOGY IMPROVES.
- NO COGNITIVE DECLINE. IN MOST PATS. SEIZURES ARE UNDER CONTROL WITH AED..
- NEUROPATHOLOGICAL CHANGES ARE NOT PROMINENT.
- MAJOR GENE INVOLVED: CSTB ON CHROMOSOME 21. IT ENCODES CYSTATIN B, INHIBITOR OF CYSTEINE PROTEASES , STRONGLY RELATED TO LYSOSOMES . (REF PENNACHIO)
- A SECOND LOCUS HAS BEEN IDENTIFIED ON CHROMOSOME 12.
- PATHOGENESIS: NOT UNDERSTOOD. NO CURE.

PME 6

THE NEURONAL CEROID LIPOFUSCINOSIS .

IT AFFECTS YOUNG CHILDREN PREVIOUSLY HEALTHY, PRODUCING A SEVERE REGRESSION AND NEUROLOGIC DERANGEMENT, MYOCLONUS AND SEIZURES ARE PRESENT.

NEURONAL AND EXTRANEURONAL DEPOSITS OF AUTOFLUORESCENT PIGMENT .
WHEN EXAMINING THIN SECTIONS (EM) , ONE CAN SEE: GRANULAR OSMIOPHILIC DEPOSITS, CURVILINEAR PROFILES AND FINGERPRINTS BODIES. THE TYPE AND AMOUNT OF THESE DEPOSITS VARIES FROM ONE CASE TO ANOTHER DEPENDING ON THE INVOLVED MUTATION

GENETIC FORMS: CLN1, CLN2,CLN3,CLN5,CLN6,CLN7, CLN8 AND CLN10 .
CLN2 MUTATION IS VERY AGGRESSIVE AND INTRACTABLE WITH AED. ON THE OTHER HAND, CLN3 MYOCLONUS APPEARS LATE AND TENDS TO BE DISCRETE .

CLN1
8-19 MO. IRRITABILITY AND RAPID PSYCHOMOTOR DETERIORATION. MYOCLONIC JERKS AND OTHER TYPE OF SEIZURES APPEAR. HAND-TWISTING. PROGRESSIVE DETERIORATION. DEATH AT YOUNG AGE.// SOME PATIENTS WITH THIS MUTATION MAY SHOW A LATE APPEARANCE OF SYMPTOMS (40 YEARS).
EM: GRANULAR OSMIOPHILIC DEPOSITS (GRODS).
CLN1 ENCODES A PALMITOYL PROTEIN THIOESTERASE (PPT1) A LYSOSOMAL ENZYME **(NEURONAL VESICULAR TRANSPORT)** THAT REMOVES PALMITATE RESIDUES FROM PROTEINS. WHEN CLN1 FAILS, THESE ACCUMULATE AS GRODS. PPT1 IS ALSO SEEN IN PRESYNAPIC NONLYSOSOMAL COMPARMENTS. VESA ET AL

CLN2
2-4 YEARS-OLD. SEVERE MYOCLONIAS AND SEIZURES. WITHIN 3 YEARS PATIENTS HAVE SUFFERED SEVERE NEUROLOGIC DETERIORATION INCLUDING BLINDNESS. SPASTICITY AND VEGETATIVE STATE PRECLUDES DEATH (ADOLESCENCE).
EEG SHOWS OCCIPITAL SPIKE RESPONSE TO LOW-FREQ. PHOTOSTIMULATION . ERG SHOWS AN EARLY DETERIORATION

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EM: PURE CURVILINEAR MEMBRANE-BOUND LYSOSOMAL AGGREGATES ARE THE HALLMARK FOR CLN2 MUTATION.

CLN2 ENCODES THE LYSOSOMAL ENZYME TRIPEPTIDYL PEPTIDASE (TPP1),, A MEMBER OF THE SERINE CARBOXYL PROTEINASE FAMILY. TPP1 IS ALSO LOCALIZED TO THE GOLGI APPARATUS AND ENDOSOMES. IT NTERACTS WITH CLN5, CLN3 AND CLN8.
THESE ENZYMES REMOVE TRIPEPTIDES FROM N-TERMINI OF SMALL PROTEINS (SUBUNIT C OF MITOCHONDRIAL ATP SYNTHASE).

CLN3 .
JUVENILE FORM OF NCL (5 TO 10 YEARS OF AGE).
EARLY, CHILDREN SOW AGGRESSIVENESS, MOOD UNSTABILITY AND REMARKABLE ANXIETY.
BLINDNESS AND DEMENTIA OCCUR RAPIDLY, IMMEDIATELY FOLLOWED BY MYOCLONIAS AND SEIZURES.
EM: FINGERPRINT PROFILES.
CLN3 CAN BE DIAGNOSED SEARCHING FOR VACUOLATED LYMPHOCYTES.
CLN3 ENCODES A TRANSMEMBRANE PROTEIN THAT LOCALIZES TO LIPID RAFTS IN LYSOSOMES, ENDOSOMES,SYNAPTOSOMES, CELL MEBRANES AND MITOCONDRIA .
CLN3 ROLES:
PROCESSING MITOCHONDRIAL MEMBRANE PROTEINS (ATPase SUBNUNIT C).
REGULALTION OF LYSOSOMAL pH , LYSOSOMAL TRANSPORT OF AA, AND LYSOSOMAL SIZE.
ANTIAPOPTOTIC ROLE .
SUSTAINING GABAergic NEURONS. ETC

CLN5 .
THE FINISH VARIANT OF LATE-INFANTILE NLC: 4 TO 7 Y-O.
DEVELOPMENTAL REGRESSION. VISUAL IMPAIRMENT. ATAXIA. MYOCLONUS EPILEPSY.
GIANT VISUAL EVOKED POTENTIALS AND SOMATOSENSORY POTENTIALS
OCCIPITAL SPIKES INDUCED BY LF PHOTOSTIMULATION (CLN2)

LIPOPIGMENTS ARE DISTRIBUTED IN THE CNS AND EXTRACEREBRALLY: FINGERPRINTS BODIES, CURVILINEAR PROFILES, LAMELLAR BODIES INCLUSIONS .

CLN5 ENCODES A TRANSMEMBRANE PROTEIN THAT LOCALIZES TO THE LYSOSOME AND INTERACTS WITH CLN2 AND CLN3.
CLN3- AND CLN5-DEFFECTIVE FIBROBLASTS SHARE AN ELEVATED INTRALYSOSOMAL pH .

CLN6
THIS MUTATION HS BEEN FOUND IN ALMOST ALL ETHNICITIES.
ONSET FROM 18 MO. TO 8 YEARS OLD. (3-5 MOST CASES)
DEVELOPMENT DELAY, GAIT AND SPEECH DERANGEMENT, SEIZURES.
EM: FINGERPRINT, CURVILINEAR AND RECTILINEAR PATTERNS.
ENCODES A PROTEIN WITH SEVEN TRANSMEMBRANE DOAMINS, LOCALIZING TO THE ENDOPLASMIC RETICULUM

CLN7
ONSET: 2 TO 7 YEARS OF AGE .
PSYCHOMOTOR REGRESSION AND SEIZURES.
PERIPHERAL LYMPHOCYTES SHOW DESNE FINGERPRINT PROFILES (UNLIKE CLN3 LYMPHOCYTES).
ENCONDES A LYSOSOMAL INTEGRAL MEMBRANE PROTEIN, PROBABLY WITH A TRANSPORT FUNCTION.

CLN8
CHILDHOOD ONSET: 5 TO 10 YEARS OLD PATIENTS.
INTRACTABLE EPILEPSY FOLLOWED BY PROGRESSIVE INTELLECTUAL DETERIORATION.
OR MILD DEVELOPMENTAL DELAY IN INFANCY, FOLLOWED BY A SEVERE MANIFESTATION OF MYOCLONUS, SEIZURES, BLINDNESS AND PSYCHOMOTOR RETARDATION.
EM:GRODs,CURVILINEAR AND FINGERPRINTS PROFILES IN VARIOUS TISSUES, INCLUDING LYMPHOCYTES.
CLN8 LOCALIZE TO THE ER AND THE ER-GOLGI COMPARMENT.
IT ENCODES AN ENZYME IN THE PATHWAY OF CERAMIDE SYNTHESIS.
.

CLN10
WHEN A COMPLETE LOSS OF FUNCTION IS PRESENT A NEONATAL ENCEPHALOPATHY AND STATUS EPILEPTICUS IS PRESENT. DEATH OCCURS WITHIN FEW DAYS.
EM: ABUNDANT GRODs IN THE CNS.
IT ENCODES CATHEPSIN D, AN IMPORTANT LYSOSOMAL PROTEASE.

SIALIDOSIS

TYPE I OCCURS ANYWHERE FROM CHILDHOOD TO ADULTHOOD. MYOCLONIAS AND SEIZURES. ATAXIA IS PROMINENT . AN INTRAOCULAR CHERRY-RED SPOT STRONGLY SUPPORTS THIS DIAGNOSIS.

TYPE II IS A SEVERE INFANTILE-ONSET FORM OF SIALIDOSIS WITH: SKELETON DEFORMITIES, MYOCLONUS, INTRAOCUALR CHERRY-RED SPOT AND EARLY DEATH.

INVOLVED GENE ENCODES THE LYSOSOMAL NEUROAMINIDASE (NEU1), AN ENZYME THAT REMOVES SIALIC ACID FROM VARIOUS MACROMOLECULES IN THE LYSOSOME.

SIALO-OLIGOSACCHARIDES ARE PRESENT IN URINE.

ACTION MYOCLONUS-RENAL FAILURE SYNDROME (AMRF) .
PROTEINURIA AND GLOMERULOSCLEROSIS AT 9 YEARS OF AGE.
10 YEARS LATER (OR MORE) APPEAR NEUROLOGIC SYMPTOMS:
BILATERAL HAND TREMOR WORSENED BY ACTIVITY (ACTION).
TREMOR PROGRESSES TO MYOCLONUS, PROGRESSIVE AND DEBILITATING. SEIZURES AE RELATIVELY EASY TO CONTROL WITH AED.
DEMENTIA IS SELDOM SEEN, ATAXIA IS VERY PROMINENT.
NEPHROPATHY (GLOMERULOPATHY) IS PROGRESSIVE AND FATAL.
INTERESTINGLY ENOUGH, NEUROLOGIC MANIFESTATIONS OF AMRF ARE NOT CONNECTED TO RENAL FAILURE,THEY CONTINUE EVEN THOUGH RENAL FAILURE IS ELIMINATED BY RENAL TRANSPLANTATION.
AUTOFLUORESCENT MATERIAL APPEARS TO ACCUMULATE IN ASTROCYTES .
THE MUTANT GENE IS SCARB2/LIMP2. IT ENCODES A LYSOSOMAL MEMBRANE PROTEIN. THIS PROTEIN ESCORTS GLUCOCEREBROSIDASE FROM THE ER TO THE LYSOSOME. (GLUCOCEREBROSIDASE IS DEFECTIVE IN GAUCHER'S DISEASE.)
THUS ENZYME ALSO PLAYS A ROLE IN THE FORMATION OF LYSOSOMES AND ENDOSOMES.

GAUCHER DISEASE .

CLINICAL FEATURES: HEPATOSPLENOMEGALIA, ANEMIA, THROMBOCYTOPENIA AND PAIN REFERRED TO THE SKELETON.

GAUCHER TYPE II DISEASE INVOLVES THE CNS AND IT APPEARS EARLY AND DISPLAYS A SEVERE COURSE.

TYPE III HAS A LATE APPEARANCE AND SHOW A SLOW PROGRESSION.
PATIENTS WITH TYPE III A HAVE A RELATIVELY MILD FORM OF GAUCHER DISEASE AND A WELL DEFINED PICTURE OF PME.

LAFORA DISEASE .

LAFORA DISEASE.

1911, GUSTAVO LAFORA : AMYLACEAKORPOREN IN SEVERE EPILEPSY CASES. A GENETIC COMPONENT. PAS + INCLUSIONS.

LATE INFANCY TO ADOLESCENCE APPEARANCE.
INTELLECTUAL CAPACITIES START TO SLOW DOWN, MYOCLONIAS AND SEIZURES DEVELOP, VISUAL HALLUCINATIONS AND CEREBELLAR SIGNS APPEAR.
IN THE FOLLOWING YEARS MYOCLONIAS AND SEIZURES BECOME REFRACTORY TO AED. PATIENTS FREQUENTLY ARE IN STATUS EPILEPTICUS. DEMENTIA APPEARS AND PATIENTS COURSE IN A VEGETATIVE STATUS. DEATH OCCURS AT EARLY AGE.
STRIANO ET AL 2008 .

NEUROPATHOLOGY HALLMARK : NEURONS AND CELLS FROM LIVER, MUSCLE AND SWEAT GLANDS SHOW DISTINCTIVE PAS + INCLUSSIONS.

THESE INTRACYTOPLASMIC INCLUSSIONS ARE MADE OF POLYGLUCOSANS (INSOLUBLE GLYCOGEN, LACKING THE SYMMETRIC BRANCHING OF GLYCOGEN) .

LAFORA DISEASE .

IN THE CNS THESE INCLUSSIONS ARE WIDELY DISTRIBUTED, HOWEVER THEY ARE NOT EQUALLY DISTRIBUTED .
SOMA, DENDRITES AND AXONES CONTAIN LAFORA BODIES.

LAFORA BODIES TYPE I AND LAFORA BODIES TYPE II.

LAFORA DISEASE IS RELATED TO MUTATIONS OF:
EPM2A (LAFORIN) , IT POSESSES A CARBOHYDRATE-BINDING DOMAIN THAT BINDS GLYCOGEN OR POLYGLUCOSAN AND A DUAL-SPECIFICITY PHOSPHATASE DOMAIN .

EPMA2B (MALIN) , AN E3 UBIQUITIN LIGASE, TARGETS: GLYCOGEN SYNTHASE, GLYCOGEN DEBRANCHING ENZYME, PTG (GLYCOGEN SYNTHASE ACTIVATOR PHOSPHATASE PP1, TO THE GLYCOGEN MOLECULE) AND **LAFORIN** .
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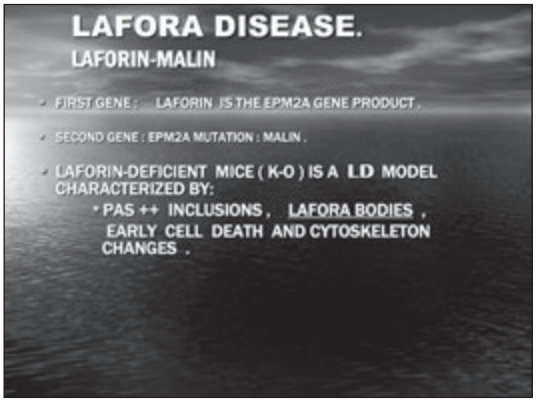
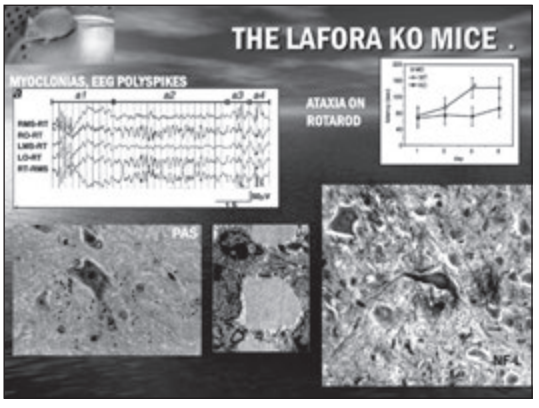
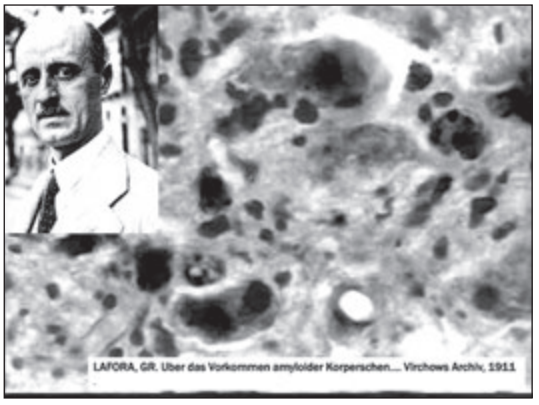
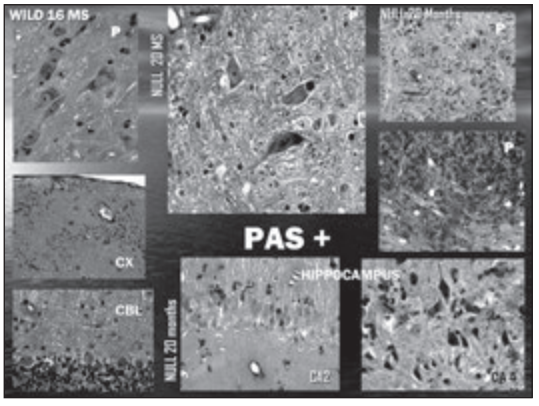





LAFORA, GR. Uber das Vorkommen amyloider Korperschen.... Virchows Archiv, 1911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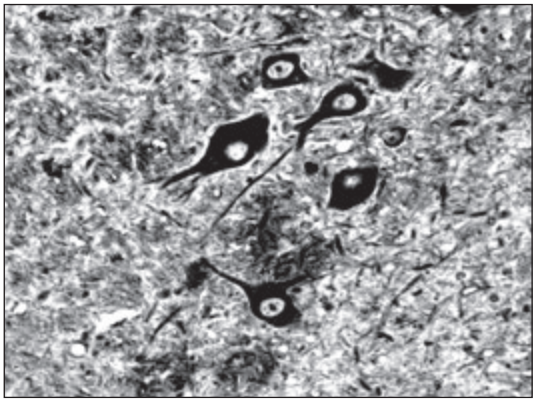

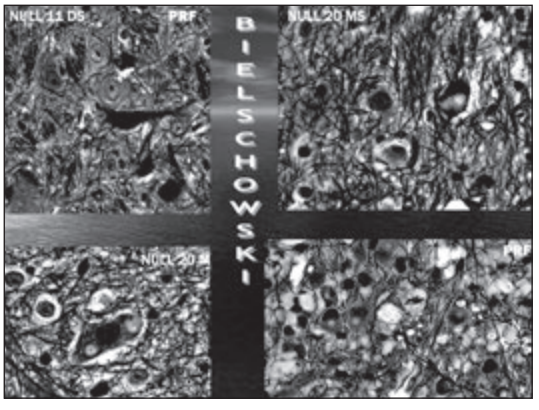
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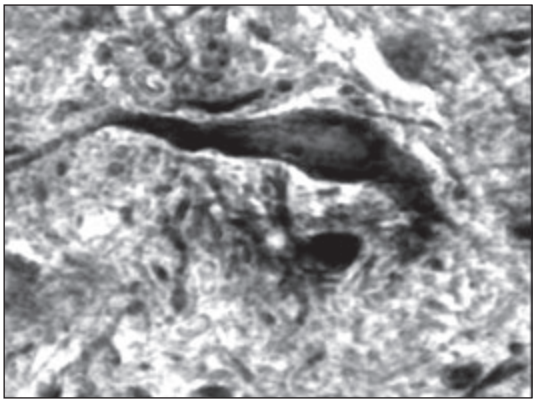
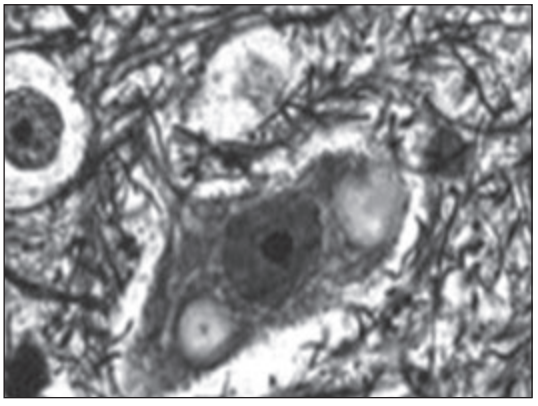
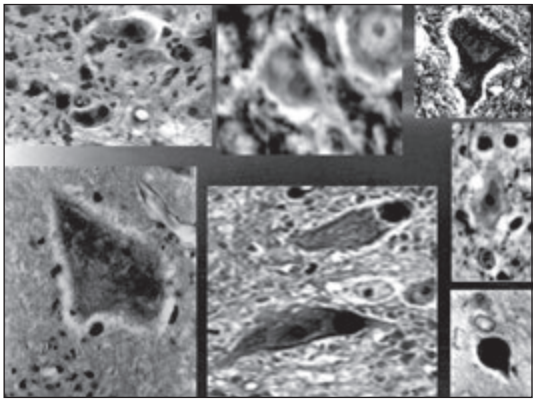
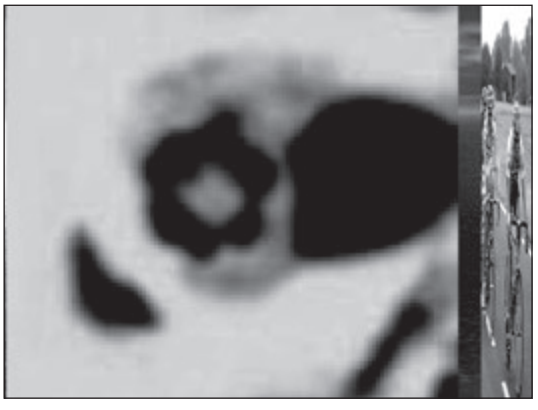
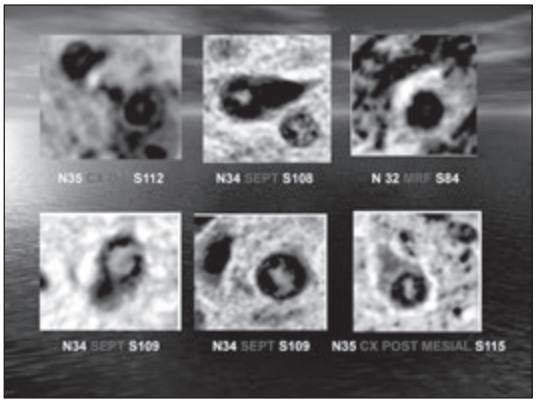
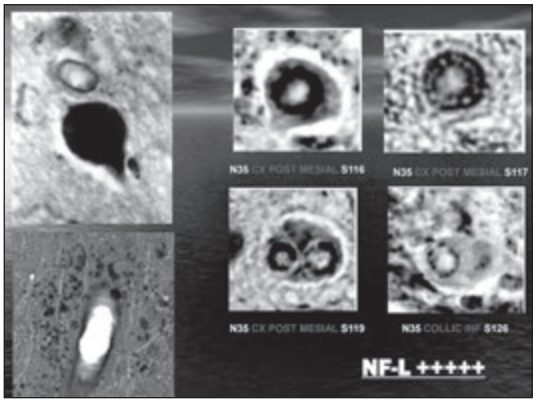


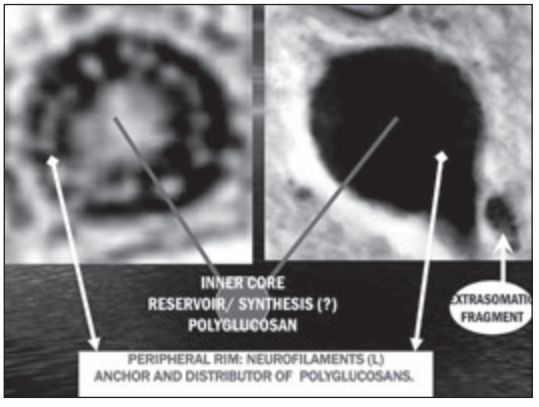












CONCLUSIONS

1) EPMA2A MUTATION REPLICATES L.D. IN MICE, WITH NEURODEGENERATIVE CHANGES AND EARLY CELL DEATH W/O LAFORA BODIES. LF BS APPEAR TO NOT BE NEUROTOXIC .
2) MALIN, THE SECOND L.D. GENE, INTERACTS WITH LAFORIN AND UNDER A LAFORIN-DEPRIVED SITUATION , MALIN STIMULATES POLYGLUCOSAN FORMATION AND ACCUMULATION .
3) WE POSTULATE THAT LAFORA BODIES TYPE II ARE COMPLEX AND METABOLLICALLY ACTIVE STRUCTURES, SOURCE OF POLYGLUCOSAN FRAGMENTS , WITH A CENTRAL CORE AND A PERIPHERAL RIM FORMED BY NF-L .

Fernando Cendes (Brazil)

FOCAL EPILEPSIES: PROGRESSIVE DISORDERS?

Epilepsy as a Progressive Disorder

Fernando Cendes, MD, PhD

University of Campinas - UNICAMP,
Campinas - SP, Brazil

Epilepsy as a Progressive Disorder

- There is evidence that some types of epilepsy progress over time, and an important part of this knowledge has derived from neuroimaging studies.

Coan & Cendes. Epilepsy Behav. 2013

Epilepsy as a Progressive Disorder

- Different studies have demonstrated structural damage more pronounced in individuals with a longer duration of epilepsy, and others have been able to quantify this progression over time.
- However, other studies have failed to demonstrate progression, possibly due to the heterogeneity of individuals evaluated.

Epilepsy as a Progressive Disorder

- Currently, TLE associated with HS is regarded as a progressive disorder.
- Conversely, for other types of epilepsy, the evidence is not so clear.
- The causes of this damage progression are also uncertain although there is consistent evidence that seizure is one of the mechanisms.

Epilepsy as a Progressive Disorder

- The conflicting data about epilepsy progression can be a challenge for daily clinical decisions for an individual patient.
- Studies with homogenous groups and longer follow-up are necessary for appropriate conclusions about the real burden of damage progression in epilepsies.

- William Gowers (1881): "seizure beget seizure"
  - Epilepsies as progressive disorders
  - Progression related to seizures

"Seizures beget seizures"

- When and why?
- How does it affect (or should affect) our decisions facing a patient with epilepsy?

Current evidence of epilepsy progression

- It can be verified or described as the worsening of seizure control, cognition, behavior, structural abnormalities, and EEG patterns as well as social interactions over time.
- Overall, it is not possible to say that all types of epilepsy are progressive conditions.

Current evidence of epilepsy progression

- While some epilepsy syndromes are clearly progressive, others do not appear to progress over time,
- and yet it is unclear if in some localization-related epilepsies, the progression of damage depends on the underlying etiology, seizure type, duration and frequency of seizures, other environmental factors (e.g., viral infections and head trauma).

Current evidence of epilepsy progression

- For example,
  - prolonged focal seizures,
  - prolonged generalized seizures,
  - isolated or clusters of brief seizures,
  - or seizures with a longer seizure-free interval
- may have distinct effects on brain integrity.

➢ **Natural history of epilepsies: controversies**

Progressive	**Not progressive**
- Tendency to progressive reduction of seizure-free intervals in populations without treatment	-Untreated population: no unfavorable evolution
-Worse prognosis of seizure control related to the number of seizures prior to treatment	-Tendency of worsening over time related to inherent severity of the disease
Reynolds E. H. Epilepsia 1987 MacDonald BK, et al. Ann Neurol 2000	Berg AT, et al. J Clin Neurophysiol 1997 Placencia M, et al. Epilepsy Res 1993

Epilepsy progression and response to AEDs

- Community-based studies of patients with several years of delay before starting AED therapy show similar patterns of response than studies with newly diagnosed epilepsies.

Feksi et al., Lancet 1991; Placencia et al., Epilepsy Res 1993

Response to AED

- One of the best prognostic factors in epilepsies is the response to the first trial of AED
- About 60% will respond to the first 2 AEDs
- ~4% with further AED trials

Kwan P, Brodie MJ. N Engl J Med 2000;342:314–19
Dlugos DJ et al. Neurology 2001;57:2259–64

Epilepsia 2010; 51:783-8

FULL-LENGTH ORIGINAL RESEARCH

Proton MRS may predict AED response in patients with TLE

*Bruno A. G. Campos, *Clarissa L. Yasuda, †Gabriela Castellano, *Elizabeth Bilevicius, *Li M. Li, and *Fernando Cendes

*Department of Neurology, †CPA, University of Campinas—UNICAMP, Campinas, São Paulo, Brazil; and ‡Institute of Physics, University of Campinas—UNICAMP, Campinas, São Paulo, Brazil

Summary

Purpose: To compare relative N-acetylaspartate (NAA) measurements in temporal lobe epilepsy (TLE) patients with good response to the first trial of antiepileptic drugs (AEDs) (an important prognostic factor) to TLE patients who failed the first AED monotherapy and required further AED trials with monotherapy or polytherapy.

Methods: We studied 31 consecutive TLE patients who responded to first AED (responders) and 21 who did not (failure-group), as well as 27 controls. Patients were seen regularly in our Epilepsy Service and underwent electroencephalography (EEG) investigation, high-resolution magnetic resonance imaging (MRI), and single-voxel proton MR spectroscopy. Voxels were tailored to the medial temporal region on each side and involved the anterior hippocampus.

Results: Analysis of variance (ANOVA) demonstrated significant variation of NAA/creatine (NAA/Cr) values in both hippocampi, ipsilateral and contralateral to the EEG focus ($p < 0.001$ and $p < 0.021$) across the groups. Pairwise post-hoc comparisons showed reduced NAA/Cr in both hippocampi of failure-group compared to controls ($p < 0.001$) and compared to responders ($p < 0.05$), but not between the controls and responders. Individual analysis showed NAA/Cr ratios lower than 2 SDs (standard deviations) below the mean of controls in 9 of 21 patients (42.8%) in the failure-group (8 with unilateral and 1 with bilateral reduction) but in none of the responders.

Discussion: These results indicate that patients with TLE who respond well to the first AED have significantly less evidence of neuronal and axonal damage/dysfunction compared to those who are refractory to the first AED trial.

KEY WORDS: 1H-MRS, Temporal lobe epilepsy, Seizures, Antiepileptic drugs.

Three groups were assigned to study:

- (1) Normal controls;
- (2) patients with TLE who responded to the first AED trial (**responders**); and
- (3) patients with TLE who failed to respond the first AED trial and required other AEDs either in monotherapy or polytherapy (**failure-group**).
  - We considered treatment failure a seizure frequency equal to or greater than 3 complex partial seizures per year or the occurrence of any secondary generalized seizure

Campos et al. Epilepsia 2010; 51:783-8

Methods

- We considered treatment failure a seizure frequency equal to or greater than 3 complex partial seizures per year or the occurrence of any secondary generalized seizure
- MRI examination was performed 1–2 years after initiation of AED therapy.

Table 1. Clinical aspects from first AED response and first AED failure groups

	First AED responders	First AED failures
n	25	21
Age (years)	37.16 (±13.4)	35.09 (±9.28)
Gender		
Male	11 (44%)	11 (52.38%)
Female	14 (56%)	10 (47.62%)
EEG side of TLE		
Right	7 (28%)	9 (42.9%)
Left	15 (60%)	9 (42.9%)
Bilateral	3 (12%)	3 (14.2%)
HA	17 (68%)	18 (85.7%)
Age at onset (years)	18.3 (±12.2)	13.4 (±9.6)
Duration (year)	8.8 (±4.2)	11.7 (±5.3)

± in parentheses indicate number of standard deviations.
There were no significant differences between the two groups for data presented in this table. HA, hippocampal atrophy..

Campos et al. Epilepsia 2010; 51:783-8

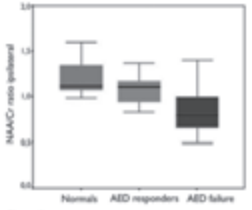


Figure 3.

NAA ipsilateral

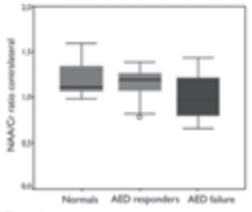


Figure 4.

NAA contralateral

Campos et al. Epilepsia 2010; 51:783-8

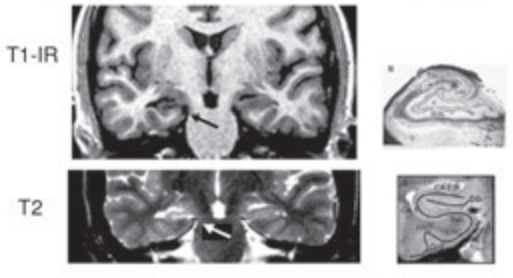
Discussion

- This difference could be related to **more extensive epileptogenic damage** caused by more severe initial precipitating injuries.
- These findings could make it possible to determine prospectively who among patients with TLE has a better prognosis and who will most likely fail to respond to AEDs.

Neuroimaging for the prediction of response to treatment in epilepsy

- The application of neuroimaging extends beyond the identification of epileptogenic lesions and the refinement of surgical interventions.

MRI provides a marker for a known histopathological process of unknown etiology



Unsolved mysteries / discrepancies

- MRI signs of HS – best indicator of surgical prognosis, however, there are patients
  - with MRI signs of HS and excellent **seizure control** ("benign MTLE" *Nat Rev Neurol 2011*)
  - with MRI signs of HS **without** seizures (in the context of familial MTLE)
  - **Without** MRI signs of HS who are **refractory** (negative MRI) and have **poor surgical prognosis** as a group
    - Why these patients do not show progressive hippocampal atrophy over the years?


Neurology

Hippocampal abnormalities and seizure recurrence after antiepileptic drug withdrawal

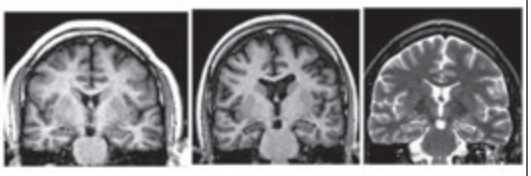
Abstract—The authors performed hippocampal volumetry and T2 relaxometry in 84 consecutive patients with partial epilepsy from a protocol for antiepileptic drug (AED) withdrawal after at least 2 years of seizure control. Seizure recurrence after AED withdrawal was more frequent among patients with hippocampal atrophy and abnormal hippocampal T2 signal.

NEUROLOGY 2006;67:134–136

T.A.M. Cardoso, MD, PhD*; A.C. Coan, MD*; E. Kobayashi, MD, PhD; C.A.M. Guerreiro, MD, PhD; L.M. Li, MD, PhD; and F. Cendes, MD, PhD

- **84 consecutive patients seizure free for >2years undergoing AED withdrawal**
- **Hippocampal volumetry and T2 relaxometry**
- **Seizure recurrence was more frequent among patients with HA and abnormal T2 signal**

Examples of MRIs from 3 patients with seizures controlled by AED

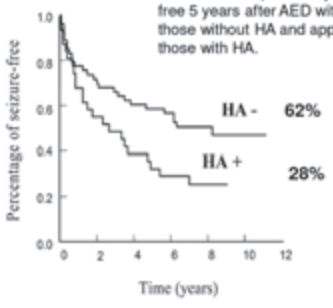


HA and seizure recurrence after AED withdrawal

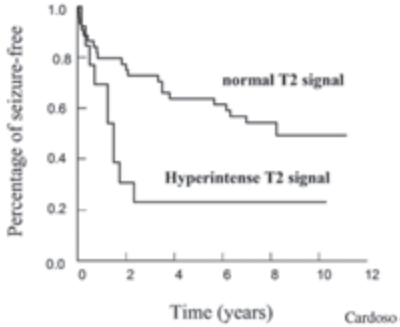
- A total of 50/84 patients (59.5%) had seizure recurrence after AED withdrawal.
- HA was present in 39/84 (46%).
- Seizure recurrence was more frequent in those with HA (p=0.01)
  - HA (29/39; 74%)
  - Normal HcVol. (21/45; 47%)

Cardoso et al

The estimated probability of remaining seizure free 5 years after AED withdrawal was 62% for those without HA and approximately 28% for those with HA.



Cardoso et al



Cardoso et al

CME

Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy

E. Kobayashi, MD; I. Lopes-Cendes, MD, PhD; C.A.M. Guerreiro, MD, PhD; S.C. Sousa, RN; M.M. Guerreiro, MD, PhD; and F. Cendes, MD, PhD

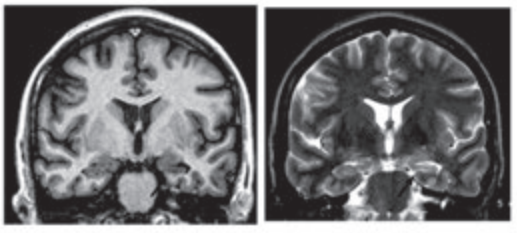
NEUROLOGY 2001;56:166–172

Hippocampal atrophy in FMTLE (n=84)

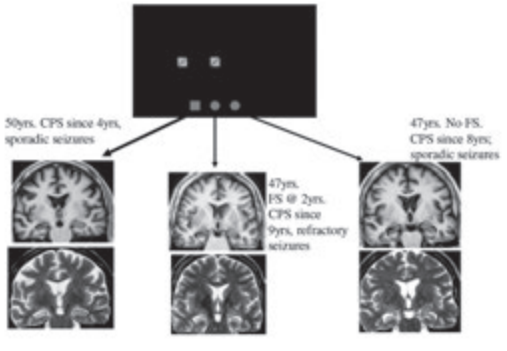
- MRI evidence of MTS in 57%
- including:
  - patients with seizure remission (46%);
  - patients with good seizure control (51%);
  - patients with refractory TLE (100%)
- HA was also found in 42% of family members who had a single or a few seizures and did not fulfill the criteria for TLE

Kobayashi et al. Neurology 2001

Familial Mesial TLE



43 years old woman, had a single seizure at 7 yrs (complex partial -> GTCS)



Archives of Neurology 2002; 59: 1891-1894

ORIGINAL CONTRIBUTION

Magnetic Resonance Imaging Evidence of Hippocampal Sclerosis in Asymptomatic, First-Degree Relatives of Patients With Familial Mesial Temporal Lobe Epilepsy

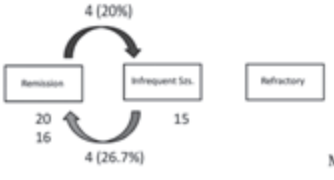
Eliane Kobayashi, MD; Li M. Li, MD, PhD; Iscia Lopes-Cendes, MD, PhD; Fernando Cendes, MD, PhD

- 52 asymptomatic individuals were studied
- we found MRI evidence of MTS in 18 (34%)
- this is against the hypothesis of seizures causing MTS

MRI and EEG as long-term seizure outcome predictors in familial mesial temporal lobe epilepsy

Conclusion

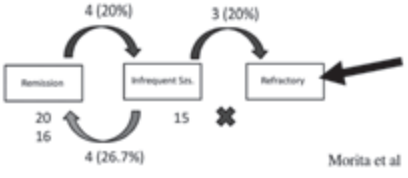
- Patients with benign FMTLE for more than two years seem to remain in the same clinical status throughout the following years (either remission or infrequent seizures), even without medication in some cases.



Morita et al

Conclusion

- Refractory patients are unlikely to achieve seizure control unless surgery is performed
- Presence of EEG IED is more frequent in refractory FMTLE patients.



Morita et al

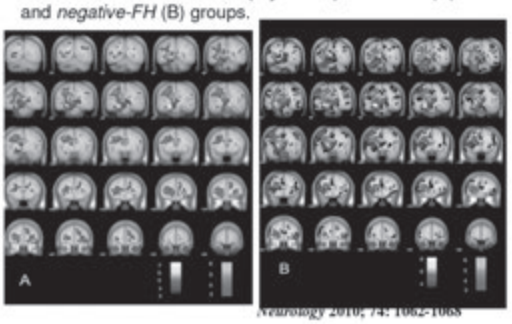
Relationship between environmental factors and gray matter atrophy in refractory MTLE

Sporadic versus MTLE with + Family history

- Sporadic-group presented a bilateral, more *widespread* pattern of atrophy and worse IQ performance.
- Probably related to a stronger environmental insults

Neurology 2010; 74: 1062-1068

Areas with GM and WM atrophy in the *positive-FH* (A) and *negative-FH* (B) groups.

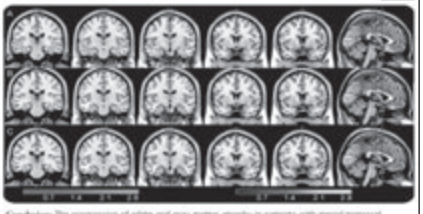


Neurology 2010; 74: 1062-1068

Sporadic versus Familial MTLE – Surgical series

- VBM preoperative analyses showed a restricted pattern of WM and GM atrophy on Family History + group, encompassing some areas within ipsilateral temporal lobe and contralateral frontal lobe;
- On the contrary, Sporadic-group presented a bilateral, *widespread* pattern of atrophy, involving areas in temporal, frontal, parietal and occipital lobes.

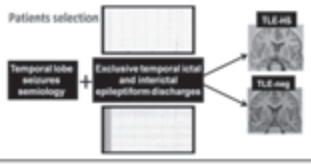
Seizure frequency and lateralization affect progression of atrophy in temporal lobe epilepsy



Conclusions: The progression of white and gray matter atrophy in patients with mesial temporal lobe epilepsy (MTLE) was more intense in patients with left MTLE and was associated with poorer seizure control and a longer duration of epilepsy. *Neurology*® 2009;73:834–842

MTLE with and without MRI evidence of HS

- 208 adult patients with clinical and EEG diagnosis of TLE (ILAE,1989)
  - 127 TLE-HS and 81 TLE-NL
- 3T MRI (T1 volumetric images)

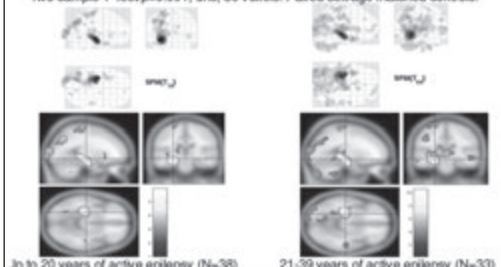


- Visual analysis, confirmed by automatic hippocampal volumetry
- 85 controls

Coan et al

VBM TLE-HS atrophy: time of active epilepsy

Two sample T-Test/p=0.001, unc, 30 voxels. Paired sex/age matched controls.

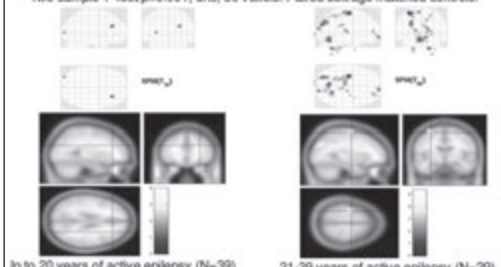


Up to 20 years of active epilepsy (N=38) 21-39 years of active epilepsy (N=33)

Coan et al

VBM TLE-NL atrophy: time of active epilepsy

Two sample T-Test/p=0.001, unc, 30 voxels. Paired sex/age matched controls.



Up to 20 years of active epilepsy (N=39) 21-39 years of active epilepsy (N=29)

Coan et al

Conclusions

- There is diffuse gray matter damage in patients with TLE-HS and TLE-NL
  - TLE-HS
    - damage is more pronounced
    - includes more importantly the hemisphere ipsilateral to the HS, bilateral temporal lobes, bilateral thalami
  - TLE-NL
    - damage is more subtle, but appears to progress over time

Progression of damage in MTLE

- Briellmann et al. showed in a group of newly diagnosed TLE patients an ipsilateral hippocampal volume decrease of 9% over a mean period of 3.5 years.
- They also verified that the hippocampal volume loss was correlated to the number of generalized seizures between the scans.

Briellmann et al. Ann Neurol 2002

Progression of damage and seizure types

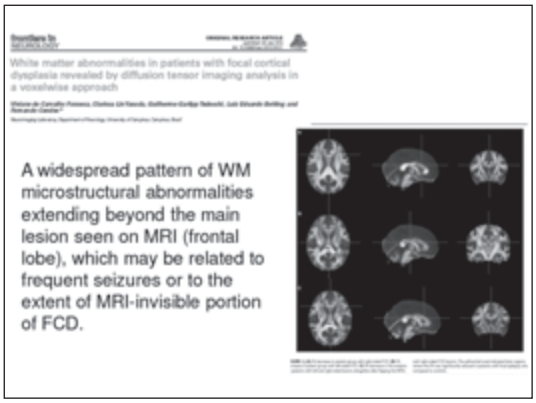
- Other studies support the hypothesis that GTCS are more harmful than focal seizures in causing damage.

Tasch et al. Ann Neurol 1999; Pulsipher et al. Epil Behav 2007

Progression of damage in IGE

- A study including patients with IGE with only tonic-clonic seizures observed that the reduction of thalamic volumes and fronto-central and limbic cortices occurred faster in patients with poorer seizure control.

Bernhardt et al. Neuroimage 2009


White matter abnormalities in patients with focal cortical dysplasia revealed by diffusion tensor imaging analysis in a voxelwise approach

A widespread pattern of WM microstructural abnormalities extending beyond the main lesion seen on MRI (frontal lobe), which may be related to frequent seizures or to the extent of MRI-invisible portion of FCD.

Avoiding seizures will also be able to block the progression of damage?

Neuronal dysfunction can improve after successful surgical treatment in TLE

- Successful removal of epileptogenic zone → postoperative NAA *increase* contralaterally and ipsilaterally, behind the resected area

Hugg et al 1995

Cendes et al 1997

Avoiding seizures will also be able to block the progression of damage?

- One study suggested that stopping seizures after surgical treatment may reverse some of the structural brain damage in TLE

Yasuda et al. 2010

Contents lists available at ScienceDirect

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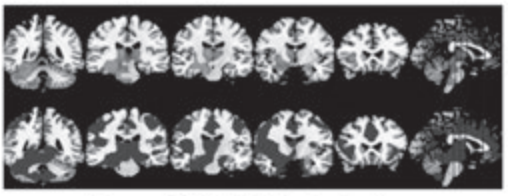
journal homepage: www.elsevier.com/locate/ynimg

Dynamic changes in white and gray matter volume are associated with outcome of surgical treatment in temporal lobe epilepsy☆

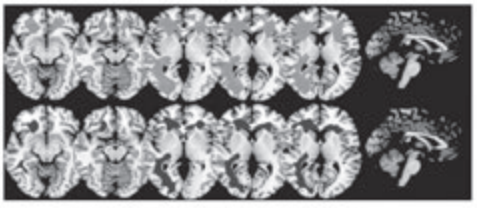
Clarissa Lin Yasuda [a,b], Clarissa Valise [c], André Vital Saúde [d], Amanda Régio Pereira [a], Fabrício Ramos Pereira [a], André Luiz Ferreira Costa [a], Márcia Elisabete Moritz [a,b], Luiz Eduardo Betting [a,b], Gabriela Castellano [c], Carlos Alberto Mantovani Guerreiro [b], Helder Tedeschi [b], Evandro de Oliveira [b], Fernando Cendes [a,b,*]

Previous MRS and PET studies have shown improvement of metabolic dysfunction after postoperative seizure control in MTLE



Pre-op MRIs: MTLE x Controls

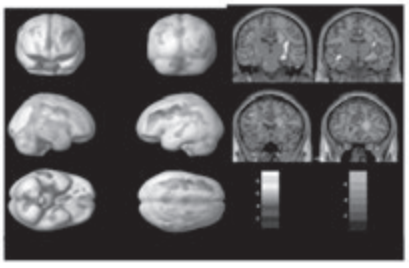
GM atrophy on seizure-free (green) and non-sz free group (red)



Pre-op MRIs: MTLE x Controls

WM atrophy on seizure-free (green) and non-Sz free group (red)

Post op GM and WM relative increase on Seizure free group



Discussion

- Different surgical outcome in MTLE may be related to preoperative subtle structural abnormalities undetected by visual analysis.
- We showed MRI evidence of reversible brain damage in MTLE patients who became seizure-free after surgical treatment.

Antiepileptic drug response in temporal lobe epilepsy

A clinical and MRI morphometry study

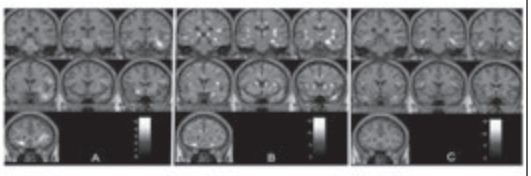
E. Bilevicius, MD
C.L. Yasuda, MD, PhD
M.S. Silva, BS
C.A.M. Guerreiro, MD, PhD
L. Lopes-Cendes, MD, PhD
F. Cendes, MD, PhD

- 165 patients with MTLE divided into 3 AED response patterns :
- 50 seizure-free (Sz-free) patients
- 87 AED-resistants
- 28 remitting-relapsing (two periods of at least one year without seizures, intercalated with a similar period of time with uncontrolled seizures despite adequate AED regimen)

Conclusions: Pharmacoresistant and remitting-relapsing groups presented a similar pattern of GM atrophy, which was more widespread compared with AED responders. Conversely, age at epilepsy onset was lower and initial seizure frequency was higher in pharmacoresistant patients.

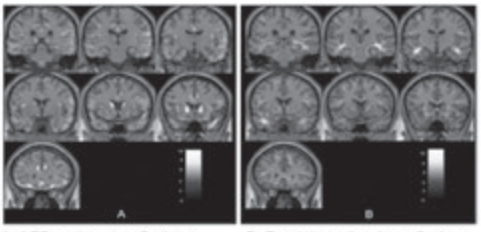
Neurology® 2010;75:1695–1701

Results – VBM (patients x controls)



A: Sz-free B: AED-resistants C: Remitting - relapsing

Results – VBM (intergroup)



A: AED-resistants x Sz-free B: Remitting-relapsing x Sz-free

Results

- Pharmacoresistants and remitting-relapsing patients presented a similar pattern of GM atrophy which was more widespread compared with AED-responders.
- Conversely, age at epilepsy onset was lower and initial seizure frequency was higher in pharmacoresistants.

Discussion

- Patients with MTLE who respond well to the first AED have significantly less evidence of neuronal/axonal damage/dysfunction than those with refractory TLE
  - **since the beginning of their epilepsy.**
- However, this confounds with the fact that MTLE is also a progressive disorder
  - **refractory seizures produce additional and progressive neuronal/axonal damage**

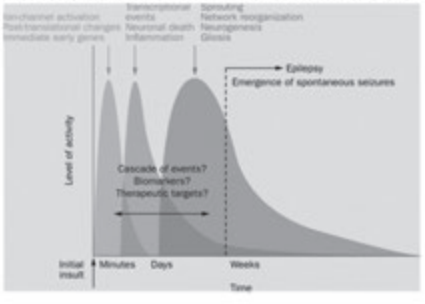
Conclusions

- AED response in MTLE is multifactorial and, according to our results, appears to be related to the underlying pattern of brain atrophy that extends beyond the hippocampus and age at seizure onset.
- **Pharmacogenetic** may be one of the additional variables in AED response

Causes of MTS

- Prolonged *status epilepticus*, severe hypoxia and limbic encephalitis, in any age, can cause MTS
  - however, only a small proportion of patients with mesial TLE have one of these antecedents
  - Outside surgical series, only a minority of MTS are associated with prior febrile seizures
- The high incidence of family history of seizures in MTLE and more studies of familial MTLE indicate a strong genetic role in the development of MTS

Maturational changes in glutamate and GABA receptor function in the developing brain - Rakhade and Jensen. *Nat Rev Neurol. 2009*



Causes of MTS

- MTS most likely have different causes
- Not all individuals with MRI evidence of MTS have refractory seizures
- However, there seems to be a variable degree of progressive damage over time, that may be, at least in part, associated with uncontrolled seizures
  - and affects regions which are connected to the hippocampus

Conclusions

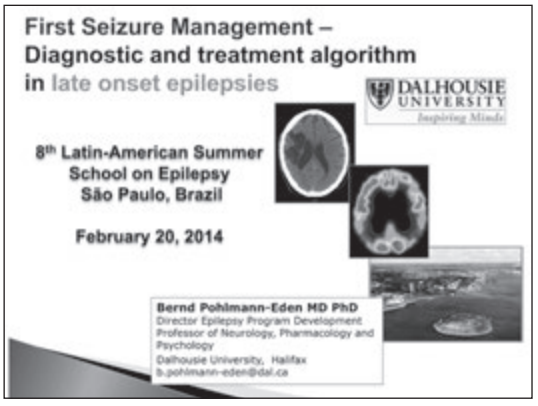
- Higher initial frequency of seizures: poorer outcome – (Sillampaă,2009)
- Neuronal damage even in AED-responders
- Refractory epilepsy is a progressive disorder
- Uncontrolled seizures: higher incidence of SUDEP
- Surgery should be indicated as early as failure to AED is detected

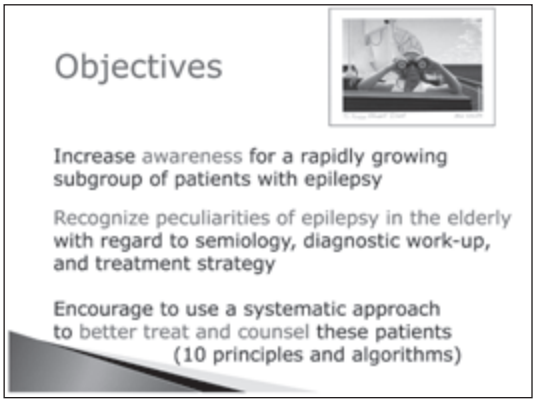
Future studies

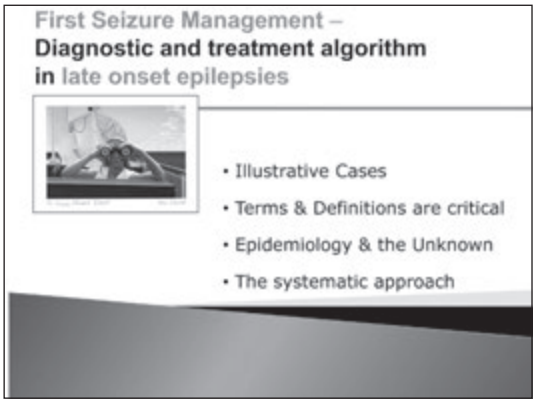
- Studies must evaluate larger series of individuals for longer periods of follow-up.
- It is important to control the genetic and environmental factors that may influence the epilepsy burden.
- Only with an appropriate multivariate analysis will we be able to have a better understanding of what is the weight of each factor in the progression of epilepsies.

Bernd Pohlmann-Eden (Canada)

FIRST SEIZURE MANAGEMENT - DIAGNOSTIC AND TREATMENT ALGORITHM IN LATE ONSET EPILEPSIES







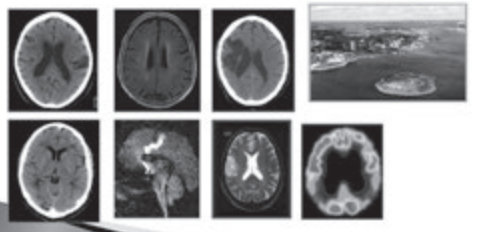
First Seizure Management – Diagnostic and treatment algorithm in late onset epilepsies

- Illustrative Cases
- Terms & Definitions are critical
- Epidemiology & the Unknown
- The systematic approach

7 Case scenarios

DALHOUSIE UNIVERSITY

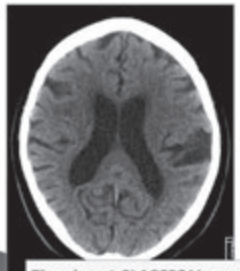
First Seizure Clinic Halifax



First Seizure Clinic Halifax

DALHOUSIE UNIVERSITY

74 y/o male



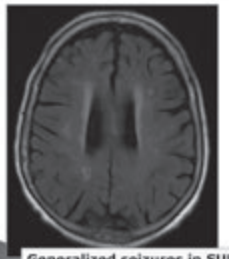
Left MCA ischemia,
since 8 mths. repeat stereotypic, short lasting **confusion** (n=7?), **not recognized as seizures** initially by FP.
EEG: Intermittent sharp wave left midtemporal.
Dx: poststroke epilepsy,
LEV BID 500mg.

The almost CLASSICAL case

First Seizure Clinic Halifax

DALHOUSIE UNIVERSITY

80 y/o female



No history of cerebrovascular disease, mild elevated blood pressure, DM.
2 GTCs within 1 week in presence of No provoking factors.

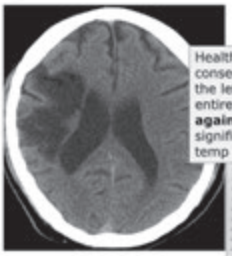
Dx? Poststroke epilepsy in presence of **advanced leukoaraiosis**?

TPM BID 50mg.

Generalized seizures in SUBCORTICAL ischemic disease

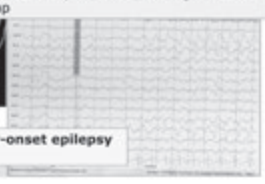
First Seizure Clinic Halifax

DALHOUSIE UNIVERSITY Inspiring Minds



65 y/o male

Healthy till age 65, right MCA 2 years ago, consecutive sensomotor hemiparesis on the left, since 2 weeks repeat SPS left entire body, no SGTCS, drug-**resistant against CBZ**, switched to LEV, no significant improvement, ETP right fronto-temp



Difficult to treat focal New-onset epilepsy after stroke (PCI-sign)

First Seizure Clinic Halifax

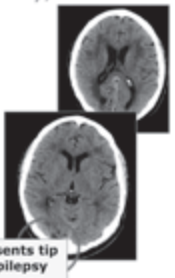
DALHOUSIE UNIVERSITY Inspiring Minds

Overall healthy 75 year old man, known hypertension, presents with **first ever witnessed nocturnal seizure**....**no** evidence for **further spells** in the beginning of the appointment, shares sexual abuse in boarding school as part of his history and then....

"I tended to see colors after being immersed in various colors in rooms in my house, particularly the shower area in the bathroom. This experience of subtle rainbow-like effects tended to make me feel euphoric and in a dream-like state which was very pleasurable and in some cases erotic"

All stereotypic, lasting 1-2 minutes, hundreds of them (SPS)

75 y/o male



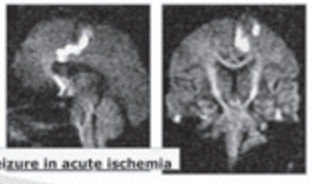
First "unprovoked" GTCS actually presents tip of the iceberg of a newly diagnosed epilepsy with frequent not recognized preceding SPS

First Seizure Clinic Halifax

DALHOUSIE UNIVERSITY Inspiring Minds

75 y/o male

First seizure with initial jerking of right leg with Jacksonian march, loss of consciousness and sGTCS followed by right-sided weakness, most prominent in the lower leg



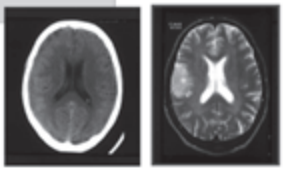
"Provoked" focal seizure in acute ischemia

First Seizure Clinic Halifax

DALHOUSIE UNIVERSITY Inspiring Minds

61 y/o male

First seizure with loss of consciousness , generalized convulsion, tongue bite, urine loss (**GTCS**) with **no focal onset** and **normal neuroexam**



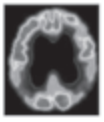
Normal CT in first seizure patients is not sufficient even wenn focal clincal signs are missing!! ALWAYS MRI!

First Seizure Clinic Halifax

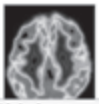
72 year old woman, diagnosed with rapidly progressive Alzheimer Disease (non genetic) and first symptoms at age 67, in nursing home since 1 year, found in the afternoon during nap time unconscious on bed, deep breathing, tongue bite, urine loss, room mate reported preceding convulsions for 1 minute, slow recovery

First unprovoked GTCS
No further occurrence for next 12 months……

72 y/o female



PET in 71 y/o female **AD patient**



Benign prognosis in sporadic seizures in Alzheimer disease

"Provoked" Seizure

Definition (ILAE)

Seizure or seizures occurring in close temporal association with an acute systemic, metabolic, or toxic insult

Prognosis is considered to be good (no seizure recurrence) reflecting acute encephalopathy

ILAE Commission
Epilepsia 38 (3): 614-618. 1997.

"Unprovoked" Seizure

Definition (ILAE)

Seizures occurring in relation to a well - demonstrated antecedent condition, substantially increasing the risk for epileptic seizures

Remote symptomatic (static)
idiopathic
cryptogenic

ILAE Commission
Epilepsia 38 (3): 614-618. 1997

"Unprovoked" – "Provoked" Seizure

Two distinct conditions?

...or just 2 conditions in a spectrum of "hidden" and more evident provoking factors...

Terms are critical

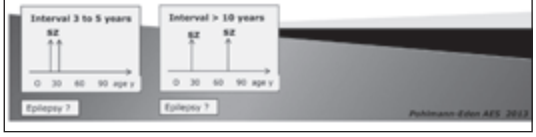
Is it as simple?

Epilepsy = "2 unprovoked seizures"

Terms are critical

Epilepsy = "2 unprovoked seizures" ?

Not clarified role of time interval between the 2 events



Diagnosis of Epilepsy after one seizure only?

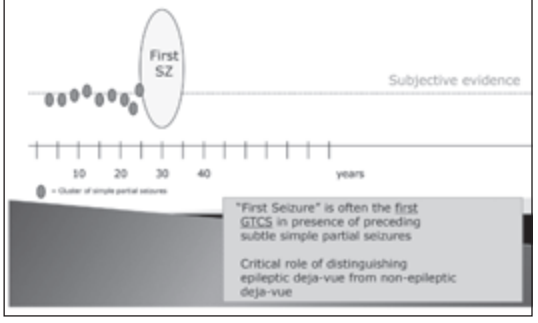
".....a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure"

* *Fisher et al. 2005: Epileptic Seizures and Epilepsy: Definitions proposed by the International League against Epilepsy (ILAE) and the International Buero For Epilepsy (IBE). Epilepsia 46: 470-472*

Terms are critical

New-onset Epilepsy
≠
Newly diagnosed Epilepsy

„First seizure" patients often have New-onset epilepsy or Newly Diagnosed Epilepsy



"First Seizure" is often the first GTCS in presence of preceding subtle simple partial seizures

Critical role of distinguishing epileptic deja-vue from non-epileptic deja-vue

Terms are critical

New-onset Epilepsy
≠
Newly diagnosed Epilepsy

"the measures have different numerators. For new onset epilepsy, the numerator includes people identified at their second unprovoked seizure. In contrast, the numerator for newly diagnosed epilepsy (NDE) includes both new onset epilepsy and people with more than two unprovoked seizures who are first diagnosed with epilepsy during the study period"

Thurman DJ et al (2011) ILAE Commission on Epidemiology: Standards for epidemiological studies and surveillance of epilepsy. Epilepsia 52(Suppl. 7):2–26

NOE defined as early stage of epilepsy

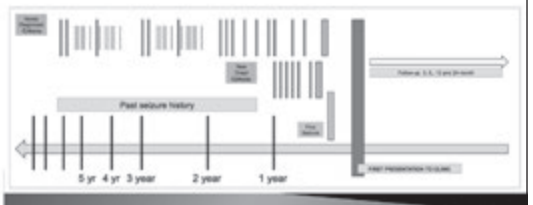
New-onset Epilepsy
subcategory
Newly diagnosed Epilepsy

NOE New-onset of epilepsy with evidence for >= 2 seizures within << 1st year
(this includes frequent preceding simple or complex partial seizures)

NDE Newly diagnosed epilepsy with evidence of ongoing seizures for >> 1 year.

Time domain suggested in the definitions of NOE and NDE, rather than the absolute number of seizures, which often is hard to assess *Pohlmann-Eden et al. 2012. Epilepsia, 53(7):1277, 2012*

Scenarios of newly diagnosed epileptic seizures
FIRST SEIZURE (FS), NOE and NDE



First Seizure Management –
Diagnostic and treatment algorithm
in late onset epilepsies

- Illustrative Cases
- Terms & Definitions are critical
- **Epidemiology & the Unknown**
- The systematic approach

What is elderly?

Tina Turner (pop star)
Photo sowing her at age
74 y/o,

Epilepsy in the elderly

> 60 years

Proportion of people ≥ 65 years
within the general population

1990 **2025**

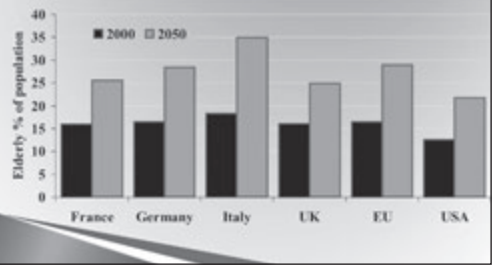
Estimated change of age distribution over time

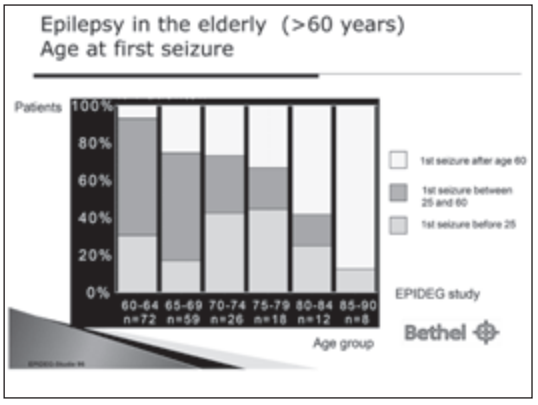
Osmanlıoğlu et al. 1993 (in: Krämer, G.: Epilepsy in the Elderly, 1999)

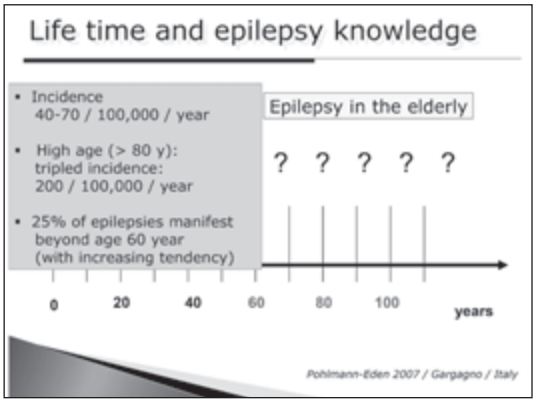
Proportion of Elderly
from the total Population

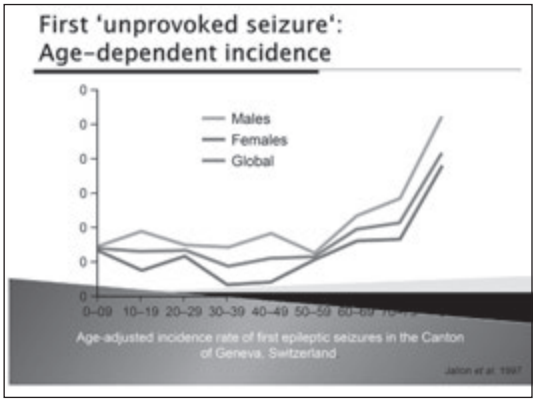
Courtesy: Alexander Krämer 2007, School of Public Health Bielefeld

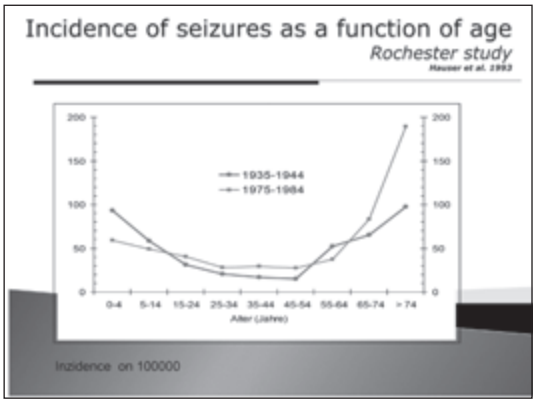
School of Public Health
Univ. of Bielefeld




Epilepsy in the elderly (>60 years)
Age at first seizure
Patients
100%
80%
60%
40%
20%
0%
60-64 n=72
65-69 n=59
70-74 n=26
75-79 n=18
80-84 n=12
85-90 n=8
Age group
1st seizure after age 60
1st seizure between 25 and 60
1st seizure before 25
EPIDEG study
Bethel

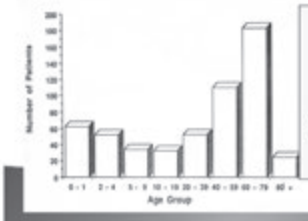

Life time and epilepsy knowledge
• Incidence 40-70 / 100,000 / year
• High age (> 80 y): tripled incidence: 200 / 100,000 / year
• 25% of epilepsies manifest beyond age 60 year (with increasing tendency)
Epilepsy in the elderly
? ? ? ? ?
0
20
40
60
80
100
years
Pohlmann-Eden 2007 / Gargagno / Italy


First 'unprovoked seizure':
Age-dependent incidence
Males
Females
Global
0-09 10-19 20-29 30-39 40-49 50-59
Age-adjusted incidence rate of first epileptic seizures in the Canton of Geneva, Switzerland
Jallon et al. 1997


Incidence of seizures as a function of age
Rochester study
Hauser et al. 1993
1935-1944
1975-1984
0-4 5-14 15-24 25-34 35-44 45-54 55-64 65-74 > 74
Alter (Jahre)
Inzidence on 100000

Epidemiology Status epilepticus

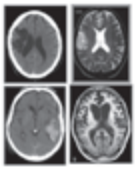
n = 546
DeLorenzo et al. 1997



Most frequent etiology
Ischaemia 22 %

Age distribution Status epilepticus

Causes of Late-onset epilepsy (the big 4)



Cerebrovascular disease
Brain tumors
Traumatic head injury
Dementia

The underlying cause of epilepsy cannot be identified in up to 50% of elderly people

Epilepsy in the Elderly

Most frequent etiologies*

Ischemia / ICH	32%
Tumour	15%
Dementia	11%
Trauma	5%
Metabolic disorder	7%
Unknown	30%*

Sanders et al. 1991

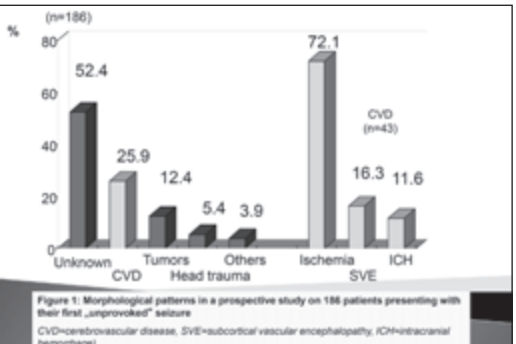


Figure 1: Morphological patterns in a prospective study on 186 patients presenting with their first „unprovoked" seizure

CVD=cerebrovascular disease, SVE=subcortical vascular encephalopathy, ICH=intracranial hemorrhage)

Pohlmann-Eden et al. 1998, Schreiner and Pohlmann-Eden 2003

Tumor associated seizures (TAS)

Ictogenesis

Ictogenesis likely to depend on **PERITUMORAL** changes (tumor-to-brain interface)
Core tumor rarely represents the seizure onset zone

Onset zone is more frequently associated with

- Receptor changes (GABA A, glutamate)
- Disruption of intercellular communication and integrity (disturbed blood– brain barrier, or altered expression of connexins)
- Chemical alterations (like pH, ionic imbalance, amino acid changes)

Clinical rule of thumb:
The higher the tumor is differentiated (ganglioglioma) the more likely to be associated with epileptogenicity, the more aggressive and less differentiated (glioblastoma) the better the seizure prognosis

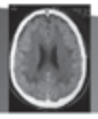
Dementia and Epilepsy in the Elderly

Alzheimer's dementia most frequent cause

Seizure occurrence more in advanced stage

Relationship / mechanisms unresolved

Most important DD: vascular dementia



Pohlmann-Eden and Eden 2010

Seizures in AD (Alzheimer Dementia)

Pohlmann-Eden and Eden. Dementia and Epilepsy.
In: The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. 2011

- Seizures only occur sporadically
- Commonly present as generalized tonic-clonic seizures
- Excellent "treatment " prognosis
- More frequently in

  a) advanced stages of late-onset AD
  b) in sporadic forms of AD (ApoE)
  c) in selected genetic mutations of early-onset AD
  d) in patients with Down's Syndrome

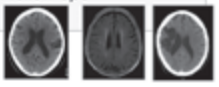
Stroke as leading cause for late-onset seizures

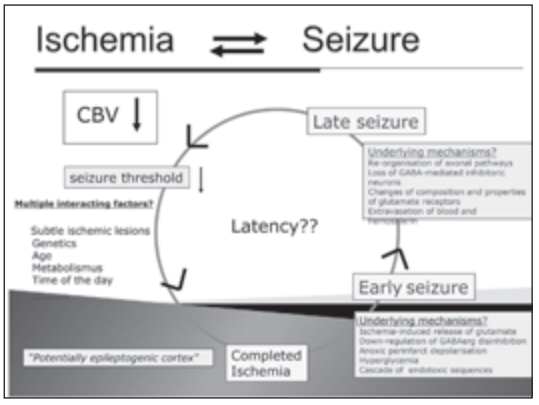
Study Dilemma

Epidemiological analysis biased and most difficult

"due to variation of study design & patient selection criteria, heterogeneity of stroke type, differences in imaging modalities, lack of distinction between seizures and epilepsy, inclusion of both early and late seizures and a high fluctuation of follow-ups"

Pohlmann-Eden et al. 1996
Pohlmann-Eden et al. 2014 (in print)





ILAE Definitions

ACUTE SYMPTOMATIC SEIZURE:
Epileptic seizure within the first 24 hrs after stroke

EARLY POSTSTROKE SEIZURE (s):
One or more seizure within the first week after stroke

LATE POSTSTROKE SEIZURE:
One unprovoked epileptic seizure
at least 1 week after stroke

POSTSTROKE EPILEPSY:
Two or more unprovoked epileptic seizures
at least 1 week after stroke

Epidemiology

Adult stroke + Seizure

Poststroke seizure (s): 2.3 [1,2] - 43.0% [3,4]

Poststroke epilepsy: 2.0 - 4.0% [5, 6, 7]

[1] Forsgren et al. Epilepsia 1996; 37: 224-229
[2] Mohr JP et al. Neurology 1978; 28: 754-62
[3] Meyer JS et al. Stroke 1971; 2: 541-554
[4] Pohlmann-Eden et al. Cer Vasc Dis 1996; 6:332-338
[5] Burn J et al. Br Med J 1997; 315: 1582-1587
[6] Bladin CF et al. Arch Neurol 200; 57: 1617-1622
[7] Lossius et al. Epilepsia 2005; 46(8): 1246-1251

Poststroke Epilepsy (PSE): Occurrence and Predictors

A long-term prospective controlled study
- Akershus Stroke Study -

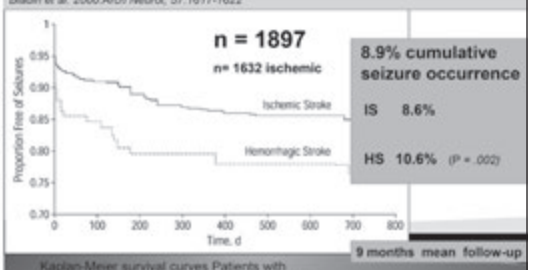
Lossius et al. 2005. Epilepsia, 46(8):1246–1251

Study comparision

2-4% poststroke epilepsy (consistent finding)

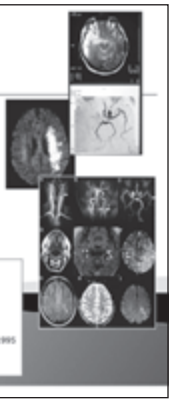
Probability of remaining seizure free after stroke - Prospective multicenter study

Bladin et al. 2000 Arch Neurol; 57:1617-1622



Kaplan-Meier survival curves Patients with ischemic and hemorrhagic stroke showing the probability of remaining free of seizures after stroke.

Reported Riskfactors for poststroke epilepsy



- Cortical[3,5,6,10] vs. subcortical location [9]
- Anterior[10] vs. posterior location[2]
- Embolic[7] vs. Thrombotic
- Borderzone infarction*
- Secondary hemorrhage*
- Thrombendarterectomy[8]
- Early[5,6,10] vs late seizure[2,3,4]
- Stroke severety[3]
- Venous infarction[11]

1) Arboix et al. 1997
2) Berges et al. 2000
3) Bladin et al. 2000
4) Fish et al. 1991
5) Kilpatrick et al. 1990
6) Labovitz et al. 2001
7) Lesser et al. 1985
8) Rangel et al. 1987
9) Schmeiser et Pohlmann-Eden 1995
10) So et al. 1996
11) Benbir et al. 2006
* Anecdotical

Proven independent Riskfactors for poststroke epilepsy

- Intracerebral Hemorrhage
- Severity of Stroke
- Cortical involvement

Lesser et al. 1985
Kilpatrick et al 1990
Arboix et al 1997
Pohlmann-Eden et al. 1997
Berges et al. 2000
Bladin et al. 2000
Lossius et al. 2005

Seizure semiology in Late-onset epilepsy

Seizures often atypical & not recognized !*

- Nonspecific prodromal symptoms
- Occur often as series or status
- "Mental slowing"
- "Black-outs"
- Dizziness
- Confusion
- "Drop attacks"

Ramsay and Pryor. Neurology 2000

Automatism & auras rare (as compared to TLE)

Prolonged focal functional deficit after poststroke seizures

Postictal hemiparesis most frequent misdiagnosis in new referrals to stroke units

14% "confusional states" > 24 h
Godfrey et al. 1982

10% Todd Parese
Norris und Hachinski 1982

21% Persistent and worsened postictal neurological deficit in (10 of 48 patients)
Bogousslavsky et al., Annal of Neurology 1992

Todd paresis mimicking re-infarction

PLED occurrence on day 3

DWI on day 1

70 year old patient with previous left MCA-infarction. Emergency admission because of deterioration of both aphasia and right hemiplegia

During further course confusion and subtle jerking of the right arm

The Unknown

We know where we are going...no worries!

The unknown journey from A to B

Clinical Epileptogenesis

- Impact of syndrome-inherent factors
- Impact of seizure activity
- Impact of therapy
- Impact of genetics
- Impact of interplay of all these factors

First Sz second Sz

Chronic Epilepsy

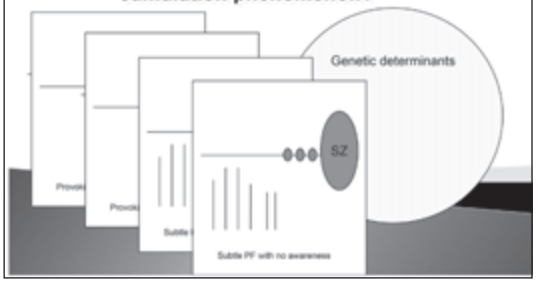
Tissue changes over time

??????

Pohlmann-Eden 2011

Seizure "Provokation"

Model: - a threshold and / or cumulation phenomenon?



Epilepsy – a progressive disease?

Experimental evidence

Primary insult

1st seizure

Lowered seizure threshold with further seizures and shortened intervals ?

?

Cellular changes & plasticity:
- change of receptors
- change of ion channels
- fos protein expression
- loss of neurons
- sprouting

Increased susceptibility for seizures?

Epilepsy – a progressive disease?

Human evidence ?

"Seizure (s) beget seizures?"

- **Shortening of intervals seizures**
- **Increased risk with subsequent seizure**

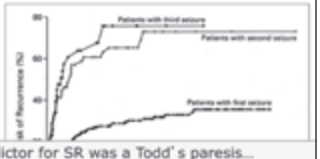
Sir William Gowers 1845–1915.

Risk of a third seizure after 2 unprovoked seizures

n = 204

Risk for SR

After 1st sz	33%
After 2nd sz	71%
After 3rd sz	73%



The only significant predictor for SR was a Todd's paresis...

Suggesting that focal brain pathology is most likely the determining variable for SR (prognosis) or the intrinsic severity

Hauser et al. NEJM, 1998

First Seizure Management – Diagnostic and treatment algorithm in late onset epilepsies

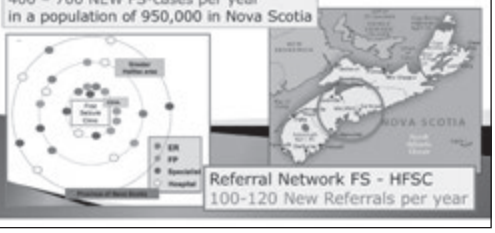
- Terms are critical
- Illustrative cases
- Epidemiology
- The systematic approach

"First Seizure" Presentations Nova Scotia

Halifax First Seizure Clinic HFSC

Epidemiology:	Incidence of First Seizures (FS)
General Population	40 – 70 / 100,000 per year

400 – 700 NEW FS-cases per year
in a population of 950,000 in Nova Scotia

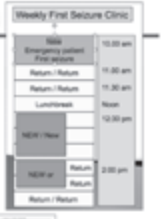


Referral Network FS - HFSC
100-120 New Referrals per year

NOE Patient population

Recruitment of subjects:

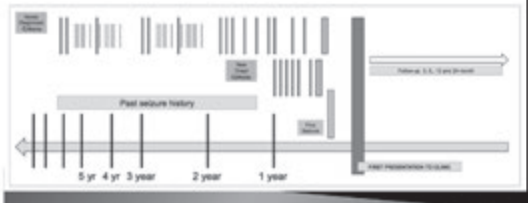
- Ascertainment source: First Seizure Clinic (FSC) Queen Elizabeth II Health Science Center, Halifax, Canada (monocentric)
- Referrals from ER, hospital admissions, outpatient clinics, GPs, specialists
- Daily triaging of referrals (BPE, KL)
- Standardized database (>100 items)
- Multimodal assessment
- Prospective cohort
- Follow-up 6, 12, 24, 48 mth

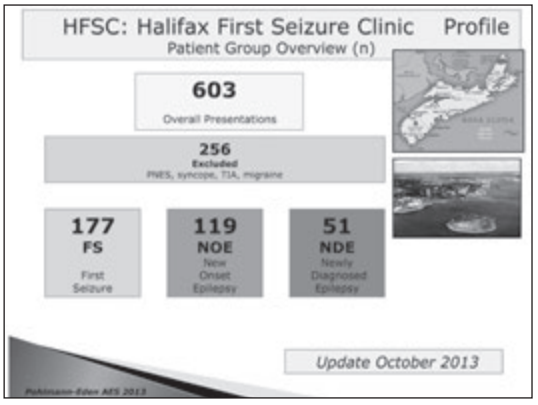


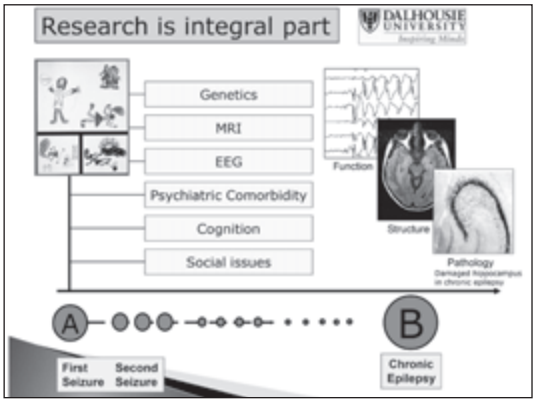
Bernd Pohlmann-Eden (MD)
Karen Legg (NP)
Candice Crocker (Res Assoc)

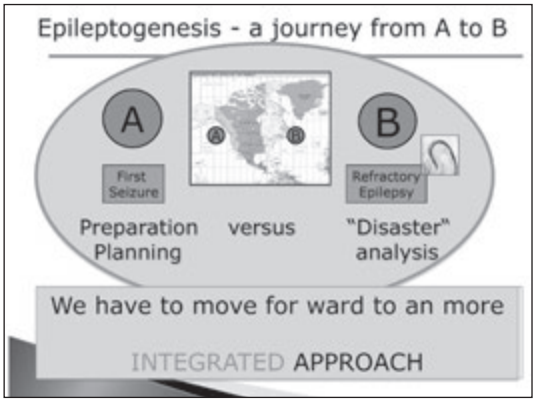
Scenarios of newly diagnosed epileptic seizures

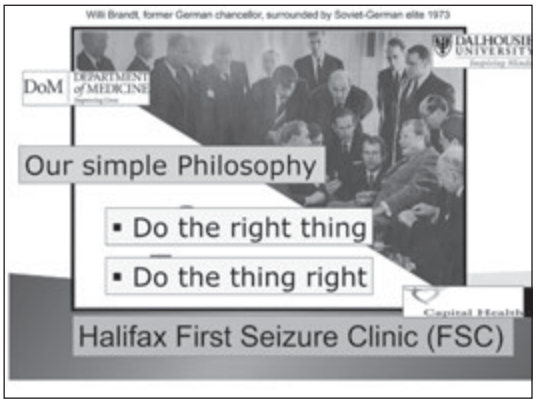
FIRST SEIZURE (FS), NOE and NDE




HFSC: Halifax First Seizure Clinic Profile
Patient Group Overview (n)
603
Overall Presentations
256
Excluded
PNES, syncope, TIA, migraine
177
FS
First Seizure
119
NOE
New Onset Epilepsy
51
NDE
Newly Diagnosed Epilepsy
Update October 2013


Research is integral part
DALHOUSIE UNIVERSITY
Genetics
MRI
EEG
Psychiatric Comorbidity
Cognition
Social issues
Function
Structure
Pathology
A
B
First Seizure
Second Seizure
Chronic Epilepsy


Epileptogenesis - a journey from A to B
A
B
First Seizure
Refractory Epilepsy
Preparation Planning
versus
"Disaster" analysis
We have to move for ward to an more
INTEGRATED APPROACH


Willi Brandt, former German chancellor, surrounded by Soviet-German elite 1973
DALHOUSIE UNIVERSITY
DoM
DEPARTMENT of MEDICINE
Our simple Philosophy
▪ Do the right thing
▪ Do the thing right
Capital Health
Halifax First Seizure Clinic (FSC)

Principle 1

- *The first "seizure" might not be a seizure*

Convulsion ǂ seizure

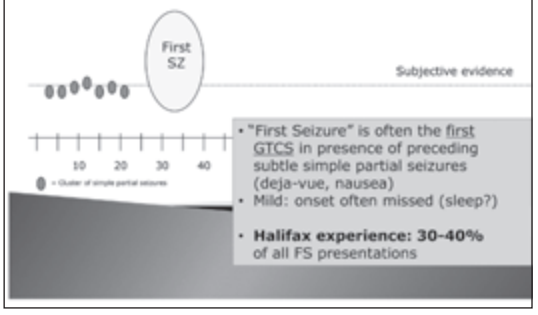
Differential diagnosis of a first "seizure"

- Syncope
- Psychogenic non-epileptic seizure
- Panic attack
- Transient ischaemic attack
- Migraine
- Hyperventilation
- Hypoglycemia
- Paroxysmal dyskinesia or dystonia

Principle 2

- *The "first" seizure may not be the first seizure*

„First seizure" patients often have New-onset epilepsy



- "First Seizure" is often the first GTCS in presence of preceding subtle simple partial seizures (deja-vue, nausea)
- Mild: onset often missed (sleep?)
- **Halifax experience: 30-40%** of all FS presentations

Principle 3

- *Explore possibly provoking factors*

Provoking factors for first seizure

Sleep disturbance
Excessive intake of alcohol
Hypoglycemia

Withdrawal medication / alcohol
Recreational drugs
Proconvulsiv medications

Proconvulsive Medication

- Antiarrhythmics (procaine)
- Neuroleptics (phenothiazine)
- Cytostatics
- Tramadol
- Aminophylline
- Antihelmincs (piperazine)
- Anaesthetics (halothane)
- Antibiotics (IV penicillin)

Principle 4

- *Perform comprehensive diagnostics*

Early EEG
Sleep-deprived EEG
High resolution MRI

Principle 4

Pohlmann-Eden B, Beghi E, Camfield C, Camfield P
BMJ 2006

Essential diagnostic procedures in patients with a first seizure

Clinical examination
Assessment of seizure semiology
Routine lab tests* (glucose, B1)
Cerebrospinal fluid**
Drug screening*
Early standard EEG, if possible within 24 hours
Sleep-deprived EEG within 1 week
High-resolution MRI

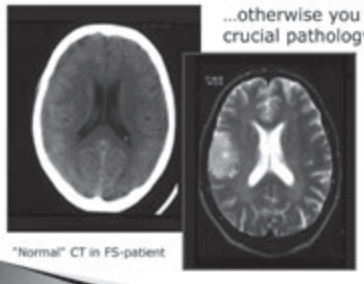
Clinical characteristics
- Rigid fall, scream
- Eyes open
- Tonic-clonic
- Duration 1-2 min max

Postictal signs
- Tongue bite
- Urine loss
- Exhaustion
- Confusion
- Muscle soreness

In agreement with "Practice Parameter AAN", based on analyis of evidence,Neurology 2007)

* depends on clinical circumstances
** if encephalitis or subarachnoid hemorrhage is suspected

MRI is the method of choice in all First-Seizure-Patients !!..*



...otherwise you may miss crucial pathology...

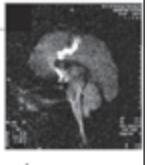
"Normal" CT in FS-patient

* Except childhood

Pohlmann-Eden et al. Ann. Neurol. 1998 (Abstract)

MRI in late-onset epilepsy

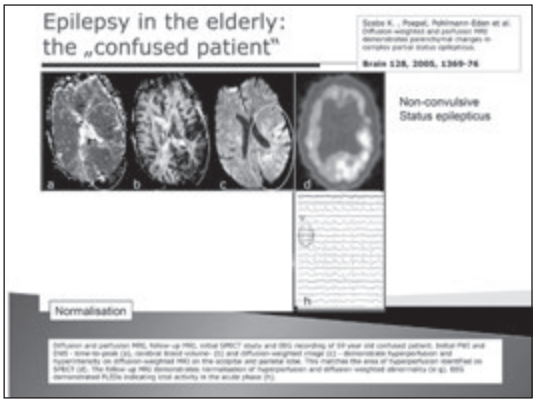
Pohlmann-Eden, Akt.Neurologie 2001

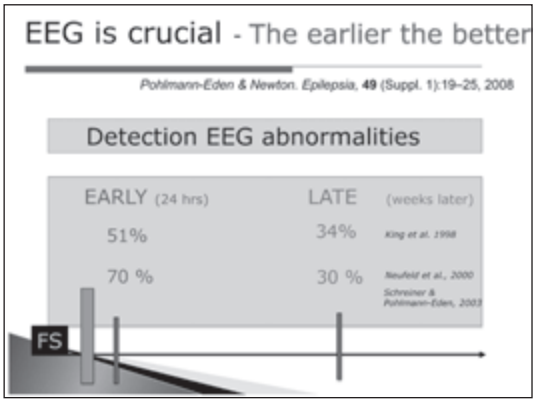


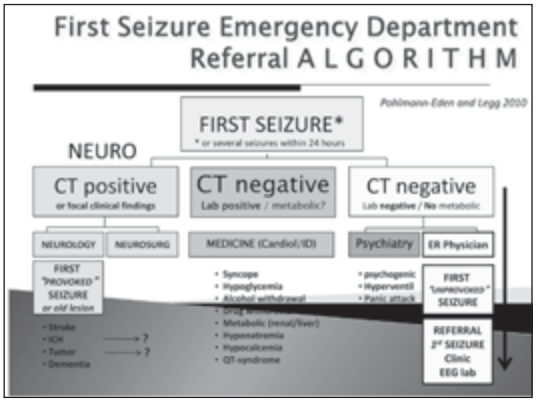
Initial MRI in ALL patients
(CT is not appropiate!)
Include MRA if possible
Protocol: DWI, FLAIR, axial and coronal

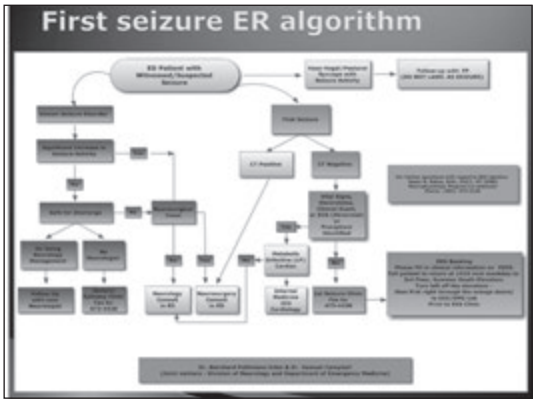
MRI- follow-up:

In all MRI-negative patients with constant or progressive focal slowing on EEG after 12 months


Epilepsy in the elderly:
the „confused patient"
Brain 128, 2005, 1369-76
Non-convulsive
Status epilepticus
Normalisation


EEG is crucial - The earlier the better
Pohlmann-Eden & Newton. Epilepsia, 49 (Suppl. 1):19–25, 2008
Detection EEG abnormalities
EARLY (24 hrs)
LATE (weeks later)
51%
34%
King et al. 1998
70 %
30 %
Neufeld et al., 2000
Schreiner & Pohlmann-Eden, 2003
FS


First Seizure Emergency Department
Referral A L G O R I T H M
Pohlmann-Eden and Legg 2010
FIRST SEIZURE*
* or several seizures within 24 hours
NEURO
CT positive
or focal clinical findings
CT negative
Lab positive / metabolic?
CT negative
Lab negative / No metabolic
NEUROLOGY
NEUROSURG
MEDICINE (Cardiol/ID)
Psychiatry
ER Physician
FIRST "PROVOKED" SEIZURE
or old lesion
• Stroke
• ICH
• Tumor
• Dementia
• Syncope
• Hypoglycemia
• Alcohol withdrawal
• Metabolic (renal/liver)
• Hyponatremia
• Hypocalcemia
• QT-syndrome
• psychogenic
• Hyperventil
• Panic attack
FIRST "UNPROVOKED" SEIZURE
REFERRAL 2nd SEIZURE Clinic EEG lab


First seizure ER algorithm

New-onset epilepsy in the elderly

Functional tests (EEG)

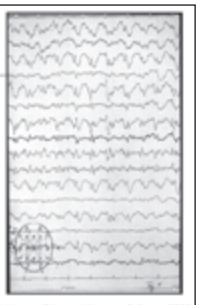
First EEG:

As soon as possible (optimal < 24h)

In any case of sudden onset of "confusion" or behavioural change

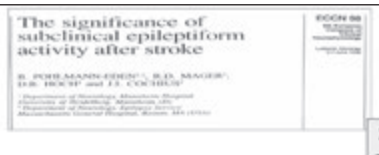
EEG-follow up tests:

After 6 and 12 months in cases of PR and / or persistent focal epileptiform activity



Pohlmann-Eden and Newton, Epilepsia 2008

Elderly patients have significantly less frequent interictal epileptiform EEG changes as compared to middle-aged and young patients.
Drury and Beydoun. Electroenc Clin Neurophys1998

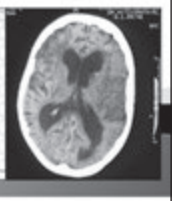


The significance of subclinical epileptiform activity after stroke

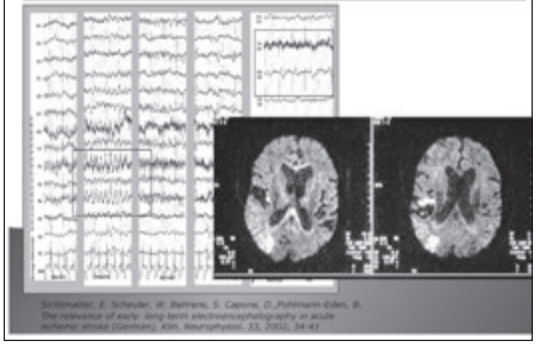
30 patients acute stroke

Serial EEG-recordings < 48 h, day 4 and day 10

30 % had initial epileptiform activity
PLEDs,
spikes, sharp waves
and SSW



Two independent epileptogenic areas on EEG in embolic stroke (own series)



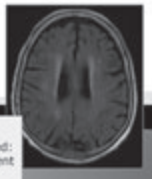
Strömaker, E. Scheuler, W. Behrens, S. Capone, D.,Pohlmann-Eden, B. The relevance of early long-term electroencephalography in acute ischemic stroke (Connect). Klin. Neurophysiol., 33, 2002, 34-41

Development of epileptiform discharges in acute stroke (early EEG-monitoring)

Pohlmann-Eden, B et al: The significance of subclinical epileptiform activity after stroke. in: Neurophysiology. Eds.: Stalberg E, Deuvaert AM, Zidar J. ; 1998, 523-532

Principle 5

- ***The first seizure in the elderly often reflects underlying cerebrovascular disease***



Implications
Cerebrovascular work work up needed:
Doppler, MRA, cardiological assessment

First Seizure in the elderly

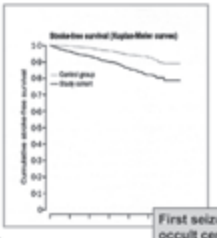
„tip of the iceberg?"

Complex scenario

Multidisciplinary work up
Doppler, Duplex, MRA,
RR, depression?

"Late-onset seizures as a predictor of subsequent stroke"

Cleary, P et al., Lancet 2004; 363: 1184-86



....highly significant difference ($p < 0,0001$) in stroke-free survival between a group of **4709 individuals** older than 60 years who presented with their "first" seizures (FS) and 4709 age and sex matched healthy controls

First seizure as initial manifestation of otherwise occult cerebrovascular disease.....

Principle 6

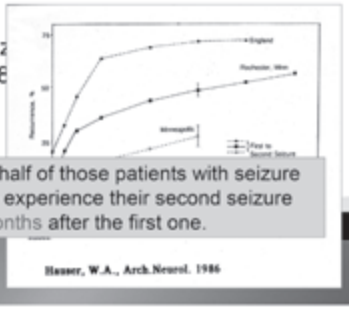
- *"Treatment" is not equal to medication*

The critical role of counseling

Explanation of seizure pathophysiology
Explanation of terms (seizure vs epilepsy)
Seizure Recurrence risk
Life style issues (sleep pattern)
Driving privileges (no driving for 6 months)
Factors to avoid (heavy machinery, working in the height, swimming in the open water)

Cumulative Risk of Seizure Recurrence and Seizure Dynamics (12 studies)

Risk of seiz
range of 28



More than half of those patients with seizure recurrence experience their second seizure within 6 months after the first one.

Hauser, W.A., Arch.Neurol. 1986

Principle 7

- *Antiepileptic treatment is rarely indicated after the first unprovoked seizure*

Stroke an exception?

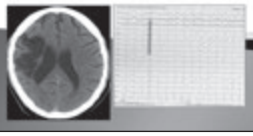
Principle 7 Exceptions

Antiepileptic treatment after after a single unprovoked seizure ?

Patients with high risk of injury from recurrent seizure

a) as polytrauma with spinal cervical fracture,
b) severe osteoporosis,
c) postictal renal failure due to myoglobulinemia
d) patients on warfarine

Patients with diagnosis of epilepsy after one seizure only



65 year old patients

Principle 8

- *Define epilepsy syndrome, if you look at new-onset epilepsy and consider treatment*

In the elderly almost aways focal (structural)

Exception de-novo-absence-status of the elderly

Principle 9

- *If treatment is started after a first seizure, the optimal length of treatment is unclear*

Principle 10

- *Treat always individually*

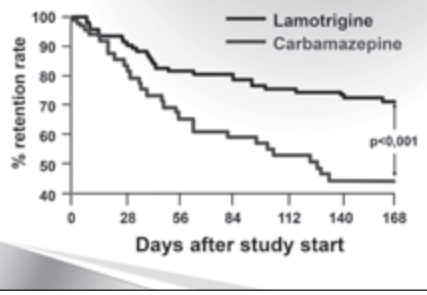
AED Studies
Epilepsy in The Elderly

Poor evidence is poor

- Only 4 studies[1,2,3,5]
- Only 2 studies double-blind[3,5]
- Treatment prognosis unclear, most likely better than in other epilepsy syndromes[4,5,6]

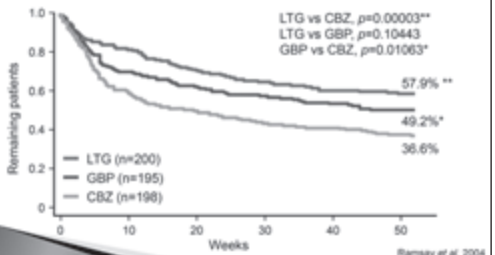
1. Cameron and Macphee 1995
2. Craig and Tallis 1994
3. Brodie *et al.* 1999
4. Stephen and Brodie 2000
5. Ramsay *et al.* 2004
6. Mattson *et al.* 1985

Lamotrigine versus Carbamazepine



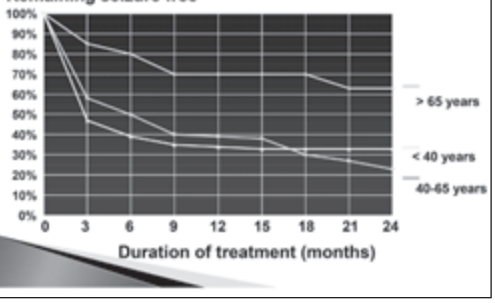
Veterans Affair Cooperative Study (VACS #428)

Retention rate (initial monotherapy)



Seizure Freedom and Age

(VA Coop. Study No. 118 [CBZ/PHT/PB/PRM])



Age-dependent AED tolerability

VA Coop. Studies No. 118 und 264

Drop-out rate (due to side effects) dependent on

Age (yrs)	%
< 40	33%
40-65	49%
> 65	64%

Treatment specifics The elderly

- Renal clearance reduced
- Hepatic clearance reduced
- Diminished intestinal absorption
- Decreased plasma protein and albumin concentration
- Drug interactions likely (frequent polytherapy)
- Increased receptor and neuronal sensitivity

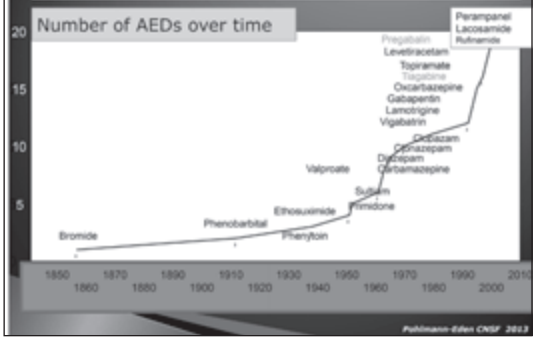
Renal Insufficiency and Antiepileptic drugs

Old AEDs : No significant changes
New AEDs: significant cumulation possible

VGB	HLT*	3–6	times
GBP	HLT	4	times
LTG	HLT	2	times
OXC	decrease	+++	clearance
LEV	decrease	++	clearance
TPM	decrease	+	clearance
TGB	increase	20%	free fraction

* Half-life time

Development of "old" and "new" AEDs
1850-2013



Pohlmann-Eden CNSF 2013

Current antiepileptic drugs:

Specific neurotoxicity* & serious side effects

*not included transient nonspecific side effects as dizziness, headache, nausea, vomiting, ataxia

Pohlmann-Eden and Legg 2013. Epileptology 1: 1-13

Pohlmann-Eden CNSF 2013

Main Criteria for AED choice

- Syndrome (focal/ generalized)
- Efficacy
- Safety profile
- Tolerability
- Low interaction profile
- Speed of action
- Age / gender
- Comorbidities
- Special issues (weight, cognition)
- Drug cost / coverage

Pohlmann-Eden AES 2013

Initiating Antiepileptic Treatment

The beginning is not always uncomplicated

Halifax couple from exchanging vows at White Point Lodge November 12, 2011

First AED choice is critical

- Drug of choice should have long-term safety, good tolerability, high seizure freedom rate, low interaction potential, allow good quality of life
- Patient might stay on the drug for a long-time
- New AEDs seem to fulfill this profile better

Interaction of antiepilepic drugs with various comedication in the elderly*

Comedication	CBZ	PTH	VPA	PB	PRM	OXC	TPH	TGB	LTG	GBP	LEV	VGB
Warfarine	+	+	+	+	+	+	+?	?	?			
Digitalis	+	+	+	+	+	+	?	+?	?			
Neuroleptics	+	+	+	+	+	?	?		?			
Antacida	+	+	+	+	+	?	?		?	?		
Antibiotics	+	+	+	+	+	?	?	?	?			

* On average 6.7 different drugs

Ramsay et al. Neurology 2004; 62 (2): 24-29

Initial treatment: Partial onset epilepsy

Center-specific preferences AED

- Lamotrigine
- Levetiracetam

- Aiming for monotherapy
- Simple treatment (BID at max)
- "Start low, go slow"
- Caution polytherapy (interaction likely)

* On average 5 to 7 drugs > 80 years

Krämer 2001, Bourdet et al. 2001, Ramsay et al. 2004

Recommended AEDs in the elderly

Specific profiles

Antiepileptic drug	Advantage	Disadvantage	Doses / day
Gabapentine	No drug interaction. Excellent tolerability, rapid titration	Weak antiepileptic drug. Strongly dependent from renal function	2–3
Levetiracetam	Strong AED, no drug interaction. Excellent tolerability, rapid titration. Low doses sufficient (1000mg?)	Rarely insomnia, behavioural disturbances Add-on only	2
Lamotrigine	Well proven minor neuropsychological impairment	Slow titration, allergic reactions, few drug interactions	2
Topiramate	Strong AED, renal and hepatic excretion, well tolerated in low doses 100mg	Few drug interactions, weight loss, cognitive impairment, titration within 3–4 wks	2
Valproate acid	'Loadable', parenteral, broad spectrum. No enzyme induction	90% protein binding enzyme inhibitor, tremor, thrombocytopathy	1*

First Seizure Management – Diagnostic and treatment algorithm in late onset epilepsies (LOE)

SYNOPSIS

Pablo Picasso at age 80 y/o

- LAO: Ischemia most frequent etiology, followed by dementia, tumors, trauma, etc.
- LAO: Semiology often atypical, postictally prolonged deficits (often mimicking restroke)
- Diagnostic Work-up has to follow a clear algorithm and ideally should include early EEG, MRI/MRA
- Treatment prognosis is overall good. Choice of AED is critical and has to be done individually tailored in the concert of age-dependent factors, comorbidities and comedication
- An overall systematic approach is encouraged with establishment of prospective data bank data

Pohlmann-Eden 2014

Epilepsy Core Group Halifax

DALHOUSIE UNIVERSITY

Dr. Mark R. Sadler	Neurologist / Epilepsy
Dr. Bernd Pohlmann-Eden	Neurologist / Epilepsy /Research
Dr. Donald Weaver	Neurologist / Research Chair
Dr. Jeremy Moeller	Neurologist / Community
Susan Rahey	Epilepsy Coordinator
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Bev Dixon	Nurse Manager
Dr. Candice Crocker	Research Coordinator
Janet Walsh	Clinical Trial Coordinator
Dr. David Clarke	Neurosurgery
Dr. Rob Brownstone	Neurosurgery
Dr. Daniel McNeely	Pediatric Neurosurgery
Dr. Michael Esser	Pediatric Neurology / Research
Dr. Paula Brna	Pediatric Neurology
Dr. Mary-Ann Hudec	Psychiatry
Dr. Ryan D'Arcy	Director NRC
Dr. Timothy Bardouille	NRC: MRI /MEG
Kirk Feindel	NRC: MRI /fMRI Research
Dr. Matthias Schmidt	Neuroradiology
Dr. Antonia Omisade	Neuropsychology
Dawnette Benedikt-Thomas	Psychometrist
Heather Smith	Social Work

Co-Directors Adult Epilepsy Program

IWK Health Centre

Capital Health

Thanks

"*Live* your questions now, and perhaps even without knowing it, you will *live* along some distant day *into* your answers"

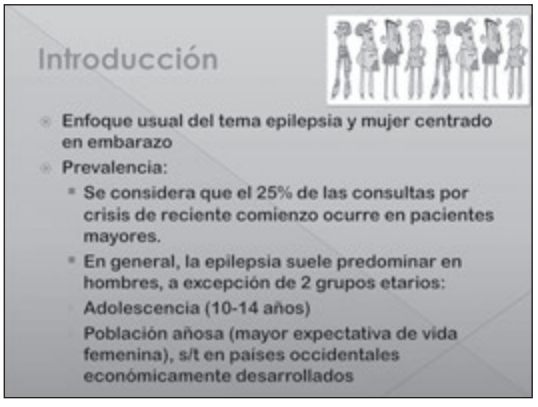
Rainer Maria Rilke

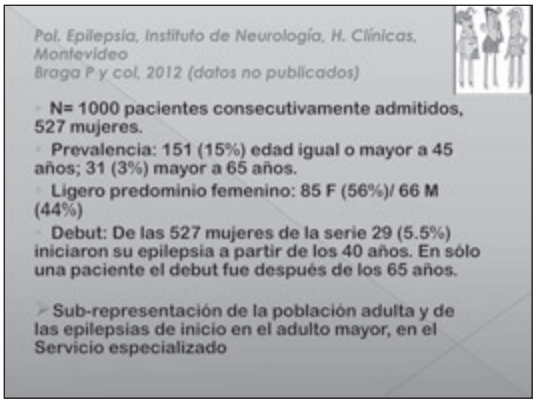
Churchlake, Nova Scotia, Canada

Contact:b.pohlmann-eden@dal.ca

Patricia Braga (Uruguay)

EPILEPSY IN ADULT AND AGED WOMEN





Alcance del tema: persistencia vs debut

	EPILEPSIA C/CRISIS PERSISTENTES	DEBUT
DIAGNÓSTICO	Conocido (cualquier tipo)	A determinar (Epi focal secundaria/ lesional)
TRATAMIENTO	Refractaria? Cirugía?	Seleccionar AED
CALIDAD DE VIDA	Creciendo con estigma; estrategias adaptativas	Nuevo desafío, adaptación

Organización de la presentación

- Desafío I: diagnóstico diferencial
- Desafío II: diagnóstico sindromático y nosológico
- Desafío III: tratamiento
- Desafío IV: pronóstico y calidad de vida

Desafíos I: diagnóstico de crisis epiléptica y diferenciales

- **Crisis epilépticas focales**
  - Las crisis con trastorno de conciencia (CPC) son más frecuentes (40% de todas las crisis en el adulto mayor)
  - Predomina origen extratemporal (frontal).
  - Son difíciles de diagnosticar por su sutileza y pleomorfismo semiológico:
    - •Referidas como mareos, o trastornos de memoria, con menos automatismos;
    - •confusión postictal más prolongada.
  - las crisis clónicas focales, versivas y tónicas bilaterales asimétricas son mucho menos frecuentes.

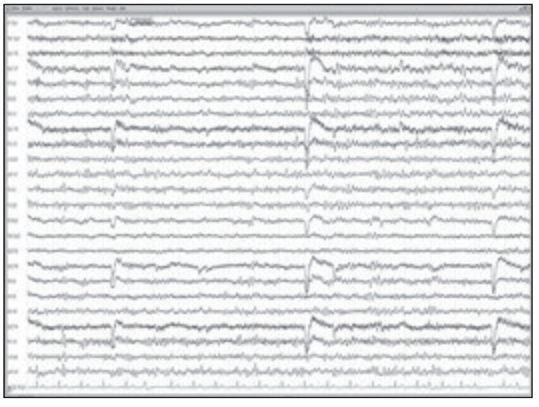
- **Crisis generalizadas primarias**
  - Estado de ausencias aislado o recurrente. S/t en mujeres mayores, muchas veces asociado a deprivación de drogas psicotrópicas.
  - Crisis de ausencia fotosensibles y ausencias con mioclonias palpebrales con franco predominio femenino

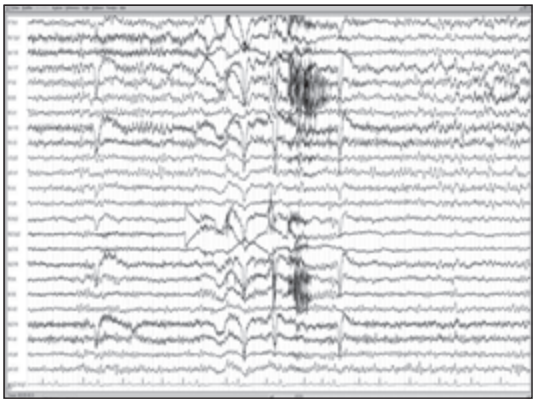
- **Crisis psicógenas**
  - Una revisión de resultados de video-EEG en adultos mayores encontró aprox 50% tenían crisis epilépticas.
  - Las crisis psicógenas fueron el tipo de evento no-epiléptico más frecuente.
  - Los episodios conversivos son más frecuentes en mujeres, en tanto que los ataques de pánico y la simulación se presentan igual en ambos sexos.

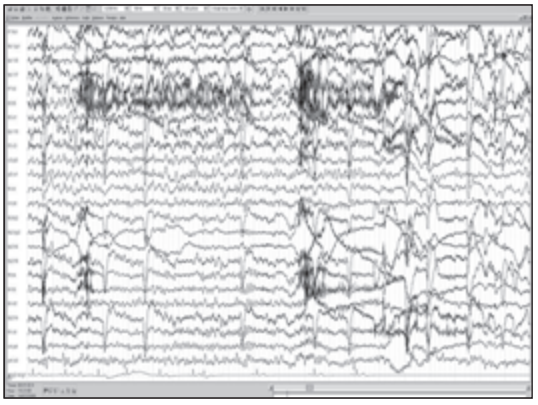
- **AIT-ACV**
  - Diagnóstico diferencial entre AIT/ACV y parálisis de Todd.
  - El fenómeno de Todd puede ser más prolongado en el paciente mayor, llevando al planteo de ACV.
  - En una serie de pacientes mayores con historia de AIT o ACV, la demora al diagnóstico de epilepsia fue de 1. 7 años.
- **Síncope**
  - DD con crisis generalizadas, eventos no presenciados
  - Síncope prolongado con fenómenos convulsivos
  - Crisis arritmogénicas

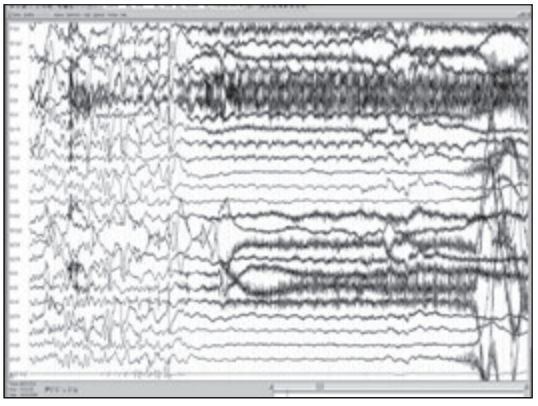
Presentación de caso
(cortesía Dra. L. Minotti, CHU, Grenoble)

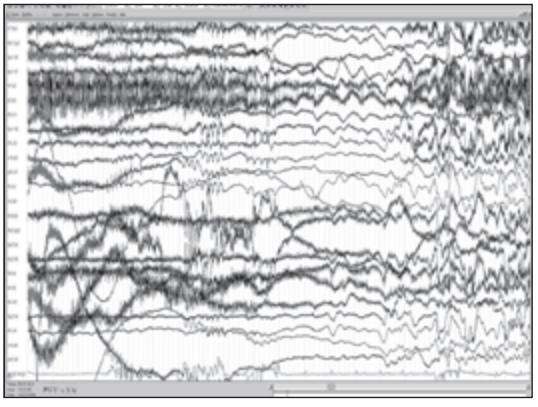
- SF, 71 años, diestra
- AP: epilepsia desde los 60 años, con auras epigástricas y crisis parciales complejas, con diagnóstico de epilepsia del lóbulo temporal, criptogenética (RMN normal).
- Tratada con DAEs: CBZ, LTG, LEV al último control.
- En los 2 últimos años agrega episodios de caída con pérdida de conocimiento, sin prodromos ni aura evidentes. Testigos refieren algunas clonias bilaterales, supraversión ocular. Recuperación rápida. Sin claro factor desencadenante identificado por la paciente.











- **Crisis arritmogénica**: aparición de una arritmia cardiaca en el curso de una crisis epiléptica parcial
- Síndrome de bradicardia ictal:
  - bradicardia
  - asistolia
  - activación de un marcapaso previamente implantado
- Prevalencia: bradicardias 5%; asistoles: 0.3-0.4%.
- Manejo:
  - Sospecha diagnóstica
  - Video-EEG-ECG
  - Evitar CBZ
  - Marcapaso
  - Mejorar el control de la epilepsia
    - Ajuste de fármacos
    - Cirugía
    - Evitar VNS

Estado epiléptico en el adulto y añoso

- forma de presentación en 30%
- Incidencia x10 veces en ≥60 años
- Incidencia 100 / 100.000 habitantes/año en >80 años
- Causas:
  - VASCULAR: ACV en la etapa aguda o debut de una epilepsia vascular asociada a una secuela remota
  - bajos niveles de FAE,
  - hipoxia,
  - trastornos metabólicos,
  - consumo de alcohol.

Cuadro confusional y estado epiléptico no convulsivo (NCSE)

De 44 ptes. mayores de 60 años enviados a EEG por confusión de origen desconocido, **7 eran NCSE, 100% mujeres**. (CHU, Grenoble)

- NCSE en persona mayor:
  - estado confusional fluctuante, sin automatismos evidentes.
  - se asocia a una mortalidad elevada
  - el tratamiento con BZD aumentaría el riesgo de muerte
- Factores pronósticos:
  - Comorbilidad, en pacientes críticos: hasta 52% mortalidad
  - Favorable (mortalidad menor a 6%) en EE secundario a bajos niveles de FAE, abstinencia alcohólica, EGI

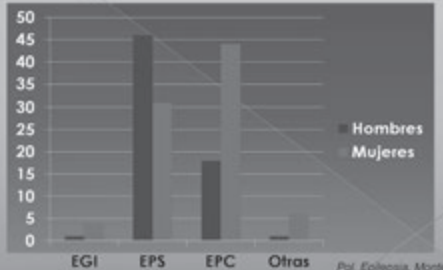
Desafío II: diagnóstico sindromático y etiológico

1. Crisis sintomática aguda o provocada

- **Trastornos metabólicos**
- **Fármacos** (10% de crisis provocadas en adulto mayor)
  - USO: adelgazantes, estimulantes cognitivos, opioides, ATB betalactámicos y quinolonas, bupropion, teofilina, clozapina, fenotiazinas, isoniacida.
  - SUSPENSIÓN brusca: BZD, barbitúricos
- Abuso o deprivación de **alcohol** y otras drogas

2. EPILEPSIAS

Distribución sindromática en hombres y mujeres de edad igual o mayor a 45 años.



Pol. Epilepsia, Montevideo. Braga P y col. 2012

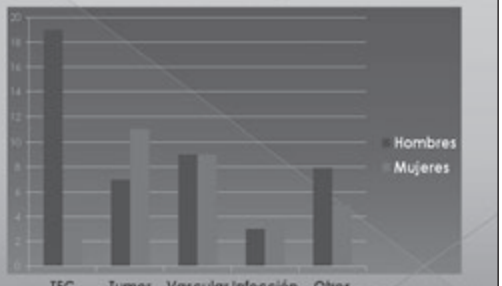
2.a. Epilepsias focales

Etiologías asociadas a la edad:

- Epilepsia vascular
- Degenerativa (12%): 9-17% de Enf Alzheimer desarrollarian epilepsia.
- Epilepsia tumoral (5-10%)
- Epilepsia post traumática (3%)
- Inmunomediadas:
  - Encefalitis límbica,
  - epilepsias con estados epilépticos inmunomediados. afecta sobre todo mujeres (93% - 12/13) con variable edad de inicio (17-69a). Edad >50 años al debut sería FR de muerte. La mayoría tenian encefalitis con antic anti NMDAR.

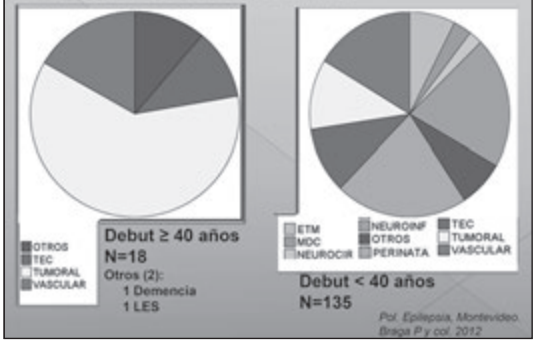
•Epilepsia criptogenética: 20 a 50% en diferentes series.

ETIOLOGÍA DE EPILEPSIAS FOCALES SINTOMÁTICAS EN MAYORES DE 45 AÑOS, SEGÚN SEXO



Pol. Epilepsia, Montevideo. Braga P y col. 2012

ETIOLOGÍA DE EPILEPSIAS FOCALES SINTOMÁTICAS EN MUJERES SEGÚN EDAD DE INICIO



Pol. Epilepsia, Montevideo. Braga P y col. 2012

Epilepsia en enf. degenerativas y demencia

- Estudios animales en roedores viejos mostraron velocidad de kindling proporcional a su performance mnésica.
- En pacientes con demencia (Alzheimer), los factores de riesgo de epilepsia fueron menor edad de inicio (4.3% <60a vs 0.55% >80a), severidad y presencia de claros potenciales epileptiformes en el EEG.
- Sub-representación en nuestra serie
  - Sesgo referencial
  - Falla diagnóstica
  - Fácil control
  - Discriminación

Etiologías de epilepsia asociadas al sexo femenino

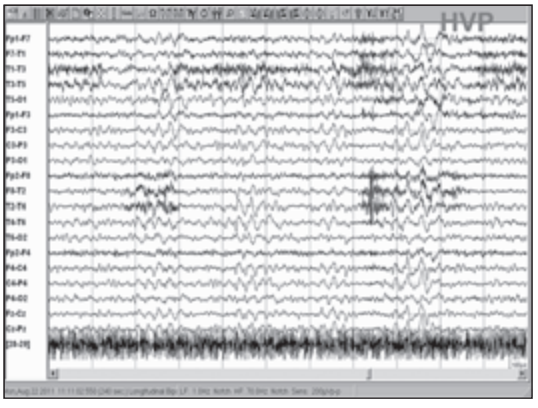
- Encefalopatías de base genética: S. Aicardi, S. Rett, Heterotopia en banda (BH, or "double cortex").
- Epilepsias con Ausencias (CAE, JAE), más frecuentes: M/F=0.7/1.
- Estados de ausencia aislados o recurrentes. Ausencias con mioclonías palpebrales
- EMJ con fotosensibilidad

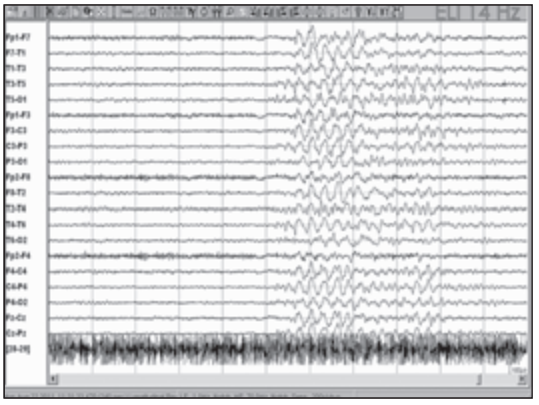
3. Epilepsias generalizadas idiopáticas

- Persistencia de EMJ
- Epilepsia mioclónica de inicio tardío
- Epilepsia con ausencias fantasma
  - Ausencias sutiles
  - CTCG que persisten en la edad adulta
  - Refractariedad
- Síndrome de Jeavons
  - Predominio femenino
  - Estados de ausencia
  - Fotosensibilidad
  - Sensibilidad al cierre ocular
  - Mioclonías palpebrales
  - Persistencia en la edad adulta

Caso clínico

- NF. SF, 71 años. Diestra. Jubilada.
- AP- Epilepsia en la juventud con crisis de ausencias. DFH que suspende hace 1 mes. Cáncer de mama 1995 (mastectomía parcial + tamoxifeno x 3 años). HTA (amlodipina). Dislipemia (estatinas).
- Emergencia por cuadro confusional con movimientos repetitivos acompañados de gestos sin patrón definido.
- EEG - presenta repetidos episodios de supraversión ocular rítmica, a veces asociados a mioclonías espinales, en correlación EEG con descargas generalizadas de complejos POL.
- Evolución: Tratada con VPA, buena evolución. Mioclonías palpebrales

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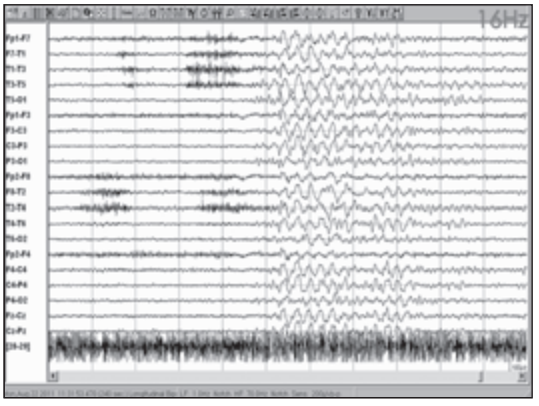
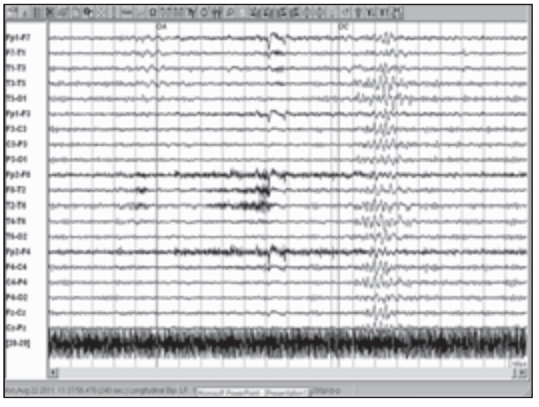
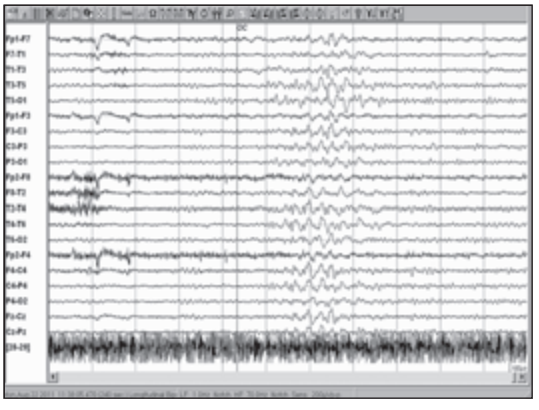

16Hz





Diagnóstico?

- Epilepsia Generalizada Idiopática con Ausencias en la infancia o juventud
- Estados de ausencia
- Persistencia de crisis en la edad adulta
- Mioclonias palpebrales
- Fotosensibilidad
- Sensibilidad al cierre ocular

⇒ **Síndrome de Jeavons**

Desafío III: Tratamiento a. Farmacológico -

- **Oportunidad:**
  - Crisis reiteradas
  - Crisis única con factores de riesgo
- **Selección de FAE**
  - ***Eficacia***
  - ***Comorbilidad***
    - -función renal,
    - -hepatopatías, función hepática
    - -APNEA DEL SUEÑO OBSTRUCTIVA: Adultos con epilepsia tienen un riesgo aumentado de OSA, que aumenta con la edad y la cantidad de FAEs, independientemente del sexo, BMI y frecuencia de crisis. – Precaución en indicación de BZD s/t en la noche.

Guidelines – ILAE, 2012

Población	A	B	C	D
Adultos, crisis focales	CBZ, LEV, PHT, ZNS	VPA	GBP, LTG, OXC, PB, TPM, VGB	CZP, PRM
Añosos, crisis focales	GBP, LTG		CBZ	TPM, VPA
Adultos, crisis generalizadas primarias			CBZ, LTG, OXC, PB, PHT, TPM, VPA	GBP, LEV, VGB *CBZ, PHT may precipitate or aggravate generalized-onset tonic–clonic seizures

- *Niveles de evidencia de eficacia/efectividad como monoterapia inicial en subpoblaciones en función del tipo de crisis y grupo etario.*

Las consideraciones de género se restringen a embarazo.

Guidelines- NICE, 2012

1.18 Older people with epilepsy

- ***1.18.1 Do not discriminate against older people, and offer the same services, investigations and therapies as for the general population. [new 2012]***
- ***1.18.2 Pay particular attention to pharmacokinetic and pharmacodynamic issues with polypharmacy and comorbidity in older people with epilepsy. Consider using lower doses of AEDs and, if using carbamazepine, offer controlled-release carbamazepine preparations. [new 2012]***

- ***Interacciones farmacológicas***

(s/t inductores enzimáticos) y otros factores farmacocinéticos

  - Warfarina, antag Ca
  - AAS, Clopidogrel (VPA disminuye la función plaquetaria) En mujeres mayores su clearance estaría disminuido en un 27%.
  - HGO
  - QT
  - TARV
  - TRH

Tratamiento farmacológico en la mujer adulta y añosa: influencia de la menopausia

- No se encontraron cambios PK en CBZ, y los hallazgos con LTG son controvertidos.
- FAEs pueden alterar el efecto de la TRH, y ésta puede influir en la frecuencia de crisis.
- Aumento en la frecuencia de crisis con TRH: estrógenos equinos conjugados y medroxy-progesterona (CEE/MPA)
- Se ha postulado que podría considerarse una combinación de 17-β-estradiol con progesterona natural
- Los preparados herbales deberían evitarse, dado que su eficacia es incierta y pueden interactuar con los FAEs.
- CEE/MPA puede disminuir los niveles de LTG
- **En suma:** seguimiento cuidadoso de mujeres que inician TRH.

- ***Perfil de efectos adversos:***

- Osteopenia y fracturas –
  - Pueden aumentar por el hipoestrogenismo en la menopausia y la asociación de FAEs inductoras del citocromo P450
  - Varios estudios muestran alteración de parámetros del metabolismo óseo en mujeres tratadas con FAEs, ya en la etapa reproductiva, pero los índices de densidad ósea descienden recién luego de la menopausia, evidenciando una prevalencia de osteoporosis mayor que en controles sin FAEs (62% vs 27%).
  - Se demostraron alteraciones en el metabolismo óseo para PHT, CBZ y VPA, no así para LTG.
  - Mayor riesgo de osteoporosis con edad, menopausia, institucionalización, varias FAEs y por largo tiempo;
  - Mayor riesgo (X2-6) de fracturas asociado a aumento de caídas en pacientes con epilepsia, ataxia.

- Caídas y fracturas

1. Por la epilepsia
   - Incidencia de caídas en pacientes ambulatorios mayores de 60 años: 16% vs 45% si enfermedades neurológicas.
   - En ambos grupos, más del 70% en mujeres.
   - Enfermedades neurológicas con mayor incidencia de caídas: ACV (89%), Parkinson (77%), demencia (60%) y epilepsia (57%)
   - Factores de riesgo: discapacidad motriz, mayor edad, sexo femenino y depresión
2. Por el tratamiento: FAEs
   - Inestabilidad en la marcha – DFH, CBZ, OXC
   - Osteoporosis

- Disminución de Inmunoglobulinas - LTG en hombres y mujeres; CBZ sólo en hombres: atención si infecciones recurrentes y posiblemente evitar en inmunocomprometidos
- Cambios de peso - VPA, CBZ, GBP, VGB vs TPM
- HipoNa – OXC, CBZ
- Signos extrapiramidales - DFH
- Trastornos psiquiátricos – LEV, TPM
- Trastornos cognitivos:
  - Sedación, disfunción ejecutiva - TODOS
  - Anomias – TPM

"Las mujeres están más predispuestas a sufrir EA a FAE"
"Las mujeres reciben más frecuentemente nuevos FAEs"

Respuesta al tratamiento y pronóstico

- El pronóstico es bueno bajo tratamiento con FAEs
- Diferentes estudios realizados en paises del primer mundo evidencian adherencia cercana al 90% y evolución libre de crisis mayor al 60%.
- En una serie argentina* de 122 pacientes con debut de epilepsia mayor a 65 años, la probabilidad de estar libre de crisis fue de 90% a los 6 meses y 67% a los 2 años. No encontraron diferencias por género.
- Predictores de crisis persistentes:
  - Más de 3 crisis al diagnóstico
  - EEG con actividad epileptiforme interictal
  - Abandono de medicación por falta de eficacia

*Besocke G y col. Epilepsy & Behavior 2012 . Outcome of newly diagnosed epilepsy in older people.

Pronóstico y cambios hormonales

- Menopausia precoz
  - fallo ovárico prematruo más frecuente
  - menopausia 3-5 años más temprana
  - asociada a mayor frecuencia de crisis / número de crisis
  - Se postula influencia de crisis y actividad interictal sobre el funcionamiento del eje hipotálamo-hipófiso-gonadal.
- Perimenopausia y control de crisis
  - datos conflictivos
  - epilepsias catameniales aumentarian la frecuencia de crisis en la perimenopausia para luego descender en la postmenopausia

b. Epilepsia refractaria y tratamiento quirúrgico

- Se ha demostrado que la cirugia de epilepsia para ELT por EH proporciona similares resultados en mayores de 50 años que en más jóvenes.
- Se ha postulado un mayor riego de deterioro neuropsicológico postoperatorio por encima de 60 años
- Hay poca información en relación a las etiologías más frecuentes de epilepsia refractaria en personas mayores, así como resultados de cirugia de epilepsia en este grupo, incluyendo diferentes etiologías y epilepsias extratemporales.
- *Conclusiones:* De las pocas series disponibles, se puede concluir que la cirugia para ELT sería eficaz en este grupo etario, y con bajo riesgo de complicaciones postoperatorias.

Cirugía de epilepsia en mujeres

- Se planteó peor pronóstico quirúrgico en mujeres, no confirmado en estudios subsiguientes.
- Estudios con MRI evidencian diferencias en la distribución y extensión de las alteraciones de la sustancia blanca en pacientes con HS según sexo.
- En mujeres adultas sometidas a cirugía de epilepsia, s/t con AP psiquiátricos no psicóticos, existe un riesgo de aparición de eventos paroxísticos motores atípicos de naturaleza psicógena en el postoperatorio, aún varios años post cirugía, e independiente del outcome de crisis.

Pronóstico vital

- Epilepsia aumenta el riesgo de neumonía comunitaria en adultos, particularmente en mayores de 65 años (OR 2.8)
- **Causas de muerte a largo plazo** en personas con epilepsia (seguimiento 18-22 años, Registro nacional, Finlandia):
  - Mortalidad aumentada en todo el seguimiento
  - Causas: enfermedades cardiocirculatorias y cáncer (s/t neoplasias del SNC – 17%-).
  - Mortalidad por IAM aumentada (HR 2.31), en ambos sexos
  - Mortalidad más prematura se debió a neoplasias SNC (mayor número de años perdidos de vida)

IV- Los grandes desafíos: calidad de vida, afectos, roles, cognición

Rol parental madre/abuela: sostén vs carga

"I was more concerned for my children and how this affected them than I was for myself. I believe this is a major concern for most mothers with epilepsy."
(The Brainstorms –Woman)

Afectivo-emocional:

- Matrimonio: las tasas de matrimonio son normales en mujeres con epilepsia (80% vs 50% en hombres; Canadá-). El establecimiento de relaciones estables puede verse afectado por la existencia previa de epilepsia. El debut de epilepsia luego del matrimonio no suele ser causal de separación en países occidentales, pero sí puede serlo (repudio) en otras culturas como la árabe.

Sexual – una minoría significativa de mujeres con epilepsia (20%-50%) tienen algún grado de disfunción sexual (libido, excitación y/o orgasmo).

Se postula rol de epilepsia *per se*, FAEs y factores psicosociales.

1. Epilepsia
   - Pacientes libres de crisis con mejor score sexual
   - Hembras que sufrieron SE post-pilocarpina mostraron menor performance sexual, sin cambios en niveles hormonales vs. controles.
2. Fármacos
   - Inductores enzimáticos asociados a menores niveles de testosterona y disfunción sexual en hombres; similar hallazgo en mujeres para motivación sexual y CBZ.
3. Psicosocial: ansiedad, depresión, estigma
   - Depresión asociada a menor score Indice de Función Sexual
   - Rasgos de personalidad, s/t introversión en mujeres asociado a disminución de SQOL.

Aspectos psico-sociales y calidad de vida:

- disminución inserción social "felt stigma".
- mayor ansiedad y depresión en mayores
- menor CV percibida si inicio tardío de epilepsia
- Mayor preocupación por las crisis, en mujeres

Independencia vs. Sobreprotección

Relación médico-papciente y comunicación

Aspectos físicos y calidad de vida

- Predictores más fuertes de CV en mujeres (QOLIE-31): perfil de eventos adversos y número de FAEs.
- Lesiones más frecuentes si epilepsia de inicio temprano
- Menopausia y TRH: influencia en control de crisis?

Pol. Epilepsia, Instituto de Neurología, H. Clínicas, Montevideo
Braga P y col, 2009 (datos no publicados)

	Preocupación por las crisis	Global	Emocional	Energía-Fatiga	Desempeño cognitivo	Efectos de medicación	Desempeño social
SEXO FEMENINO	4.2%						
MAYOR EDAD ACTUAL		5.4%			6.3%		
MAYOR EDAD AL DEBUT	7.5%						
MAYOR DURACIÓN EPILEPSIA			4.4%	5.5%			
CRISIS ACTUALES	5.0%	4.6%	9.4%	6.8%	4.7%		7.9%
ANSIEDAD-DEPRESIÓN	5.7%		4.2%		4.0%		
CRISIS PSICÓGENAS		4.7%					
EGI vs Epilepsia PARCIAL	4.6%						
HISTORIA FLIAR. EPILEPSIA			9.4%				
COMORBILIDAD Neurológica					3.8%		
MAYOR NÚMERO DAEs					4.1%	5.1%	12.5%
PREDICCIÓN TOTAL	27.0%	14.7%	27.4%	12.3%	22.9%	5.1%	20.4%

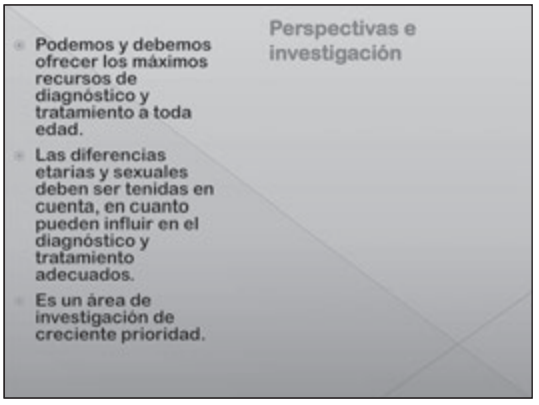
N=98. QOLIE-31

Logros profesionales, académicos y laborales en la mujer adulta.

- Crisis impredecibles
- Efectos adversos cognitivos de los FAEs
- Discriminación por sexo y enfermedad
- Crecientes expectativas personales y del entorno cultural en el rol de la mujer
- Retiro – repercusión económica, psicológica y social

Evolución cognitiva

- Evaluación cognitiva de adultos mayores con epilepsia: menor performance en todos los tests.
- Posibles predictores de deterioro cognitivo:
  - Inicio precoz de la epilepsia y mayor duración de la enfermedad
  - Mal control de crisis


Perspectivas e investigación
Podemos y debemos ofrecer los máximos recursos de diagnóstico y tratamiento a toda edad.
Las diferencias etarias y sexuales deben ser tenidas en cuenta, en cuanto pueden influir en el diagnóstico y tratamiento adecuados.
Es un área de investigación de creciente prioridad.

João Pereira Leite (Brazil)

STATUS EPILEPTICUS-INDUCED EPILEPSY: EXPERIMENTAL OBSERVATIONS

Cigden Ozkara (Turkey)

APPROACH TO MEDICALLY RESISTANT EPILEPSY

Cigden Ozkara (Turkey)

EPILEPSY SURGERY AND PRESURGICAL EVALUATION

Roberto Caraballo (Argentina)

FIREs

Febrile infection-related epilepsy syndrome (FIRES)
Síndrome epiléptico relacionado a infección febril

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SERVICIO DE NEUROLOGÍA
Hospital de Pediatría S.A.M.I.C.
"Prof. Dr. Juan P. Garrahan"

FIRES

- Definición

- FIRES es considerado una encefalopatía epiléptica severa asociada con estado de mal multifocal refractario.

FIRES

- Breve reseña histórica
- Awaya and Fukuyama (1986) describen en niños previamente normales un cuadro denominado "encephalitis-like entity".
- Posteriormente, el síndrome ha sido llamado variablemente :
  - "Severe refractory status epilepticus due to presumed encephalitis" (Sahin et al., 2001),
  - "Idiopathic catastrophic epileptic encephalopathy" (Baxter et al, 2003),
  - "New-onset refractory status epilepticus" (Wilder-Smith et al, 2005),
  - "Devastating epileptic encephalopathy in school-aged children" (Mikaeloff et al 2006),
  - "Acute encephalitis with refractory repetitive partial seizures"(Sakuma et al, 2010),
  - "Febrile infection-related epilepsy syndrome" (van Baalen et al., 2010),
  - "Fever-induced refractory epileptic encephalopathy in school-age children (Nabbout et al., 2010).

FIRES

- FIRES se presenta en niños previamente sanos y se caracteriza por tres fases:

- Una fase inicial con una infección febril simple,
- Seguida pocos días después de una fase aguda con convulsiones focales frecuentes y recurrentes que evolucionan rapidamente a estado de mal epiléptico refractario generalmente sin fiebre y sin otros signos neurológicos asociados,
- Y finalmente una fase crónica que consiste de una epilepsia refractaria y deterioro neuropsicológico (van Baalen et al., 2010).
- Estas manifestaciones se presentan en niños entre 3 y 15 años de edad, han sido descrito pacientes adultos.

FIRES

- Han sido descritos series de pacientes con esta particular encefalopatía en Japón, UK, Francia, Alemania, Italia, USA, Austria, Singapur, Argentina, y Taiwan (Caraballo et al., 2013).

FIRES

- La etiología y los mecanismos subyacentes de FIRES son aún desconocidos, y han sido propuestos factores immunológicos (Kramer et al., 2011; Specchio et al., 2011), genéticos, e inflamatorios (Nabbout et al., 2011)

FIRES
Objetivos

- Analizamos las características clínicas, electroencefalográficas, hallazgos neuroradiológicas, tratamiento, y pronóstico de 12 pacientes con FIRES.

FIRES
Material y Métodos

- Estudio retrospectivo realizado en el Hospital Juan P Garrahan de Buenos Aires de 12 niños con FIRES evaluados entre 1997 y 2012.
- Evaluamos las historias clínicas de los pacientes con un tiempo medio de seguimiento de 6.5 años (R, 1-15 años).

FIRES
Material y Métodos

- Criterios de inclusión:

- Niños previamente sanos entre 2 y 16 años de edad con desarrollo psicomotor normal;
- Convulsiones de inicio agudo, refractarias asociadas a un cuadro de encefalitis-like;
- Ausencia de gérmenes patógenos en LCR, sangre u otros fluidos orgánicos;
- y evolución a epilepsia crónica sin un período de latencia libre de anticonvulsante (Kramer et al., 2011).

- El estado de mal epiléptico fue considerado refractario si inicialmente no respondió al tratamiento con FAEs (benzodiazepinas, DHH, FB, como así también al AVP y LVT intravenosos).

FIRES
Material y Métodos

- Se excluyeron pacientes con una presentación similar debido a una encefalitis viral, encefalomielitis diseminada aguda, síndrome de Rasmussen, anormalidades estructurales o metabólicas.

FIRES
Material y Métodos

- Evaluamos antecedentes personales, historia familiar y los aspectos clínicos incluyendo semiología de las crisis y el manejo del período agudo.
- Se realizaron estudios virológicos, immunológicos, metabólicos, y genéticos. Evaluaciones Neuropsicológicas, características clínicas y manejo de la epilepsia crónica fueron también analizados.
- En todos los pacientes se evaluó en LCR, sangre y orina y otros fluidos orgánicos agentes infecciosos. En todos los casos marcadores inflamatorios en LCR y en sangre fueron investigados. Diferentes anticuerpos y test metabólicos fueron realizados. Estudios genéticos y biopsia cerebral no fueron llevados a cabo.

FIRES
Material y Métodos

- EEG interictales e ictales, TAC, RNM cerebro fueron analizadas en la fase aguda y crónica.
- Seis y cuatro pacientes tuvieron registros Video-EEG recordings in the acute and chronic phases, respectivamente.
- Todos los pacientes tuvieron RNM 1.5 T en la fase aguda y crónica y en 3 de ellos RNM 3T con protocolo de epilepsia fueron realizadas en el período crónico. PET scans no se realizó en ningún paciente y en ninguna fase.
- En la fase crónica, analizamos las características clínico-EEG, tratamiento y evolución. La conducta fue evaluada a través del informe de los padres.
- Las evaluaciones neuropsicológicas incluyeron test standar sobre CI en todos los pacientes.

FIRES
Resultados

➢ *Características generales*

- Incluímos 12 pacientes, 8 masculinos y 4 femeninos.
- Todos previamente sanos y neurologicamente normales
- Sin antecedentes personales a destacar .
- Un paciente tuvo historia famiar de CF y 1 paciente tuvo historia familiar de epilepsia.

FIRES

➢ Resultados

- La edad media y mediana de presentación fue de 8.5 y 10 años (R, 2-13.5 años), respectivamente.
- Infección de VAS y gastroenteritis asociadas con fiebre fue observada en 9 y 3 pacientes respectivamente.
- Clinical de encefalitis-like caracterizada por fiebre, cefalea, somnolencia y confusión precedieron las convulsiones por 2-10 días.

FIRES

➢ Resultados : fase aguda

- Las convulsiones fueron focales con compromiso de conciencia en todos los casos y generalización secundaria caracterizada por clonías en tres.
- Manifestaciones autonómicas tales como, palidez, apnea, y cianosis, fueron registradas en 8 pacientes. Tres pacientes también tuvieron crisis aparentemente generalizadas.
- Las crisis rapidamente aumentaron en frecuencia (28 a102, día) exacerbadas a status epilepticus dentro de 24-36 horas. Un paciente tuvo mioclonías repetitivas faciales.
- Ocho pacientes requirieron tratamiento con altas dosis de FB, DFH o midazolam, combinada con ventilación mecánica en 4 casos. La duración del tratamiento intensivo fue de 2-40 días (mediana 16 días).

FIRES

- Resultados: fase aguda

- EEG interictal (vigilia y sueño) mostró un único foco en 1 paciente, 4 focos en 2 pacientes, y tres focos en los restantes 7 pacientes. Focos bilaterales se observaron en todos, excepto en 2. Cuatro casos también tuvieron paroxismos bilaterales, uno de ellos mostró descargas epileptiformes lateralizadas, bilaterales, independientes en regiones anteriores.
- Ondas lentas difusas delta-theta se observaron en todos los casos. Un paciente mostró patrón de paroxismo-suppresión.

FIRES

- Resultados: fase aguda

- El EEG ictal incial mostró comienzo temporal en 4 pacientes (33%), frontotemporal en 4 (33%), frontal en 2 (16.5%), y frontoparietal en 2 niños (16.5%).
- Todos ellos rapidamente desarrollaron crisis multifocales e independientes. unilaterales o bilaterales, que propagaron al mismo hemisferio en 3 y al contralateral en 9, involucrando diferentes lóbulos.

FIRES

Resultados

- *Investigaciones*

- Se encontró pleocitosis en LCR en 7 de 12. Proteinas elevadas en LCR en 1 caso.
- Herpes simple 1 and 2, enterovirus, citomegalovirus, virus Epstein-Barr, coxsachie, echovirus, influenza A y B , parainfluenza, parvovirus, parotiditis, adenovirus, sarampión, y retrovirus fueron investigados.
- Serología para toxoplasma y micoplasma pneumonia también fue realizada.
- En todos los casos los tests fueron negativos.

FIRES

Resultados

- *Investigaciones*

- El estudio neurometabólico en sangre, orina y LCR fue normal en todos los casos.
- Las evaluaciones inmunológicas incluyeron: niveles de immunoglobulinas, anticuerpos antinucleares, complemento, anticuerpos anti-ADN, anticardiolipinas, beta 2 glicoproteina, anticoagulante lupus, factor reumatoideo, proteína básica antimielina, y anticuerpos antitiroides. Los resultados fueron negativos en todos los casos.
- Los anticuerpos anti-NMDAR fueron realizados en 2 pacientes, y detección de bandas oligoclonales en LCR en 6 pacientes. Todos fueron normales, excepto en 2 de seis pacientes con oligoclonales positivas.

FIRES
Resultados

- *Investigations*

- RNM fue realizada en todos los casos. Al inicio la RNM fue normal en 5 pacientes de12. Hiperintensidad en los dos hipocampos en 5 casos. En tres de ellos la region periinsular fue también afectada. Hiperdensidad en ganglios basales fue detectada en dos casos.
- La RNM en la fase crónica reveló atrofia cerebral difusa en 4, e hiperintensidad en otros 4 pacientes. La hiperintensidad fue localizada en ambos hipocampos en tres y región periinsular en 1.

FIRES
Resultados

- *Tratamiento*

- Todos los pacientes fueron tratados con Aciclovir y/o antibióticos para cubrir la posibilidad de infección del SNC.
- Todos recibieron múltiples esquemas de FAEs: incluyendo FB (12), DFH (12), benzodiazepinas (12), LVT(12), AVP (6), thiopental (6), CBZ (5), OXC (4), y TPM (6) con respuesta negativa.
- Ocho pacientes fueron tratados con barbitúricos (burst-suppression). Cinco de ellos respondieron bien temporariamente, controlando el status epilépticus.

FIRES
Resultados

- *Tratamiento*

- Diez pacientes recibieron tres veces 1.2 gr GGIV cada 10 y 14 días, excepto 3 casos quienes recivieron GGIV cada 21 días durante 4, 6, y 8 meses, respectivamente.
- Nueve pacientes recibieron esteroides en diferentes formas y dosis. La mayoría recibió pulsos de metilprednisolona (30mg/kg/día durante 5 días seguidos por oral prednisona (1 mg/kg/día). Dos pacientes y 1 paciente tuvieron buena respuesta a GGIV y corticoides respectivamente, pero la buena respuesta fue sostenidad en solo 1 caso tratado con GGIV con 50% de reducción de crisis.

FIRES
Resultados

- *Tratamiento*

- Dos casos fueron tratados con DC en la fase aguda, uno de los cuales mostró una respuesta sostenida con 50-75% de reducción de crisis. El restante caso tuvo menos de 50% de reducción de crisis.
- Un caso no respondió a la plasmaféresis. Un caso tuvo una respuesta parcial (50% reducción de crisis) a 2 dosis de rituximab, sin embargo, debió suspenderse debido a una linfopenia marcada.

FIRES
Resultado

- *Evolución*
- Todos los pacientes siguiendo la fase aguda tuvieron epilepsia y no hubo período libre de crisis siguiendo la fase aguda.
- Dos pacientes estuvieron libre de crisis luego de 18 y 25 meses de tratamiento con FAEs, respectivamente. Los restantes 10 casos presentaron epilepsia refractaria.
- Todos los pacientes presentaron crisis focales simples o complejas. La semiología de las crisis fueron definidas por el relato de los padres y del registro Video-EEG en 4 casos.
- Versión oculocefálica se registró en 4 pacientes, crisis focales tónicas y clónicas focales en 2 casos y crisis clónicas orofaciales en 1 caso.
- Crisis distónica se domumentó en dos casos y crisis autonómicas en otros dos casos.
- Episodios de inmovilidad, pérdida de conciencia asociadas con automatismos ocurrieron en 7 pacientes. Tres de ellos tuvieron auras abdominales.

FIRES
Resultado

- *Evolución*

- Cuatro pacientes de 12 presentaron convulsiones tónicas o tónico-clónicas secundariamente generalizadas.
- En dos casos las crisis tuvieron un origen multifocal.
- Tres pacientes presentaron status epilepticus focal que requieron asistencia en UTI.
- Las crisis fueron diarias en 2 casos, semanales en 1 caso, mensuales en 4 y cada 2 a 4 meses en el caso restante.
- Las crisis ocurrieron agrupadas en 5 pacientes
- Todos los pacientes tuvieron las crisis en vigilia y 4 de ellos también durante el sueño.

FIRES
Resultados

- *Evolución*

- Actualmente 10 pacientes reciben 2 o 3 FAEs.
- Dos pacientes de 12 están libres de crisis, luego de 2 y 10 años de seguimiento.
- Dos pacientes continúan en DC. Ambos continúan con crisis cada 2 a 4 meses, respectivamente.
- Tres casos continúan recibiendo GGIV sin buenos resultados.
- Cirugía fue realizada en 1 caso secundaria a lesión secuelar lóbulo temporal (esclerosis mesial). La paciente tuvo un 50% de reducción de crisis luego de 2.5 de seguimiento.
- Un caso con crisis refractaria y frecuentes episodios de status epilepticus se le implantó un estimulador vagal. Presentó una reducción del 50% de las crisis luego de 1 año de seguimiento.

FIRES
Resultados

- *Evolución*

- El EEG interictal mostró un ritmo de base lento en todos los casos y en 10 casos se observaron ondas lentas bilaterales predominantemente en región fronto-temporales.
- Todos los pacientes tuvieron espigas focales predominantes en región temporal, frontal, fronto-temporal . Ondas agudas y espiga-onda fueron registradas en 5 y 3 casos respectivamente.
- Descargas bilaterales fueron registradas en 2 pacientes. Paroxismos generalizados y ritmos rápidos focales o generalizados no fueron observados.
- Las alteraciones EEGs fueron activadas durante el sueño en 5 pacientes. No observamos cambios durante la HV.

FIRES
Resultados

- *Evolución*

- El registro EEG ictal mostró ritmos theta-delta reclutantes seguidos de ritmos rápidos en 6 casos.
- Descargas ictales caracterizadas por actividad rítmica theta-delta seguidas de espigas y espiga onda reclutantes fueron registradas en 4 casos.
- Ritmos rápidos seguidos de ondas lentas que aumentaron de voltaje y frecuencia fueron documentados en los restantes dos casos.
- Las manifestaciones EEG ictales fueron focales en 6, multifocales y unilaterales en 3 y multifocales y bilaterales en los 3 restantes casos.

FIRES
Resultados

- *Evolución*

- La RNM durante la fase crónica mostró atrofia cerebral difusa en 5, en tres de ellos fue leve y en dos severa. Dos casos tuvieron esclerosis mesial unilateral y en dos fue bilateral.
- La evaluación neuropsicológica mostró deterioro cognitivo severo en 4 pacientes, moderado en 3 y leve en 1 paciente. El nivel intelectual fue limítrofe en 2 casos y normal en 2.
- Déficit de atención y dificultad en el aprendizaje fue observado en 4 pacientes y déficit en memoria y funciones ejecutivas en 3 pacientes.
- Uno de los casos con normal CI tuvo déficit de atención asociado a problema de aprendizaje y el otro tuvo solo déficit de atención.
- Impulsividad y agresividad estuvo presente en 7 casos, siendo severas en dos de ellos.

FIRES
Discusión

- Nuestra serie de casos con FIRES presenta similares características con respecto a los pacientes publicados.
- Altas dosis de barbitúricos en la fase aguda nos permite un control temporario de las crisis.
- Dieta cetógena
- Gamaglogulinas IV
- Rituximab
- Plasmaféresis
- Estimulador vagal

FIRES
Discusión

- FIRES es un solo proceso ?
- Origen neocortical de las crisis (Lóbulo frontal)
- Pacientes con crisis refractarias (Definición de zona epileptógena)
- Tratamiento epilepsia crónica (GGIV, corticoides, DC, EV, cirugía)
- Casos con buen pronóstico (espectro clínico amnplio)
- Infección podría activar proceso inmunológico

FIRES
Discusión

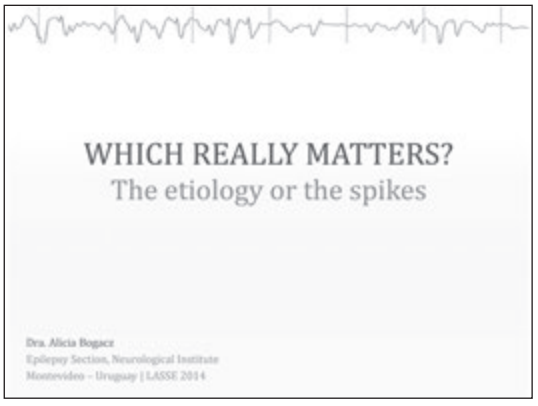
- Factores ambientales tales como, fiebre e infecciones no determinadas pueden gatillar una predisposición a epilepsia como sucede en el Síndrome de Dravet y convulsiones focales migratrices del lactante
- Déficit de Glut I
- Mutaciones en PCDH19

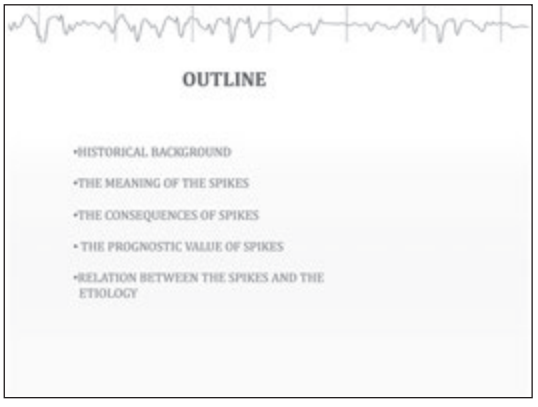
FIRES

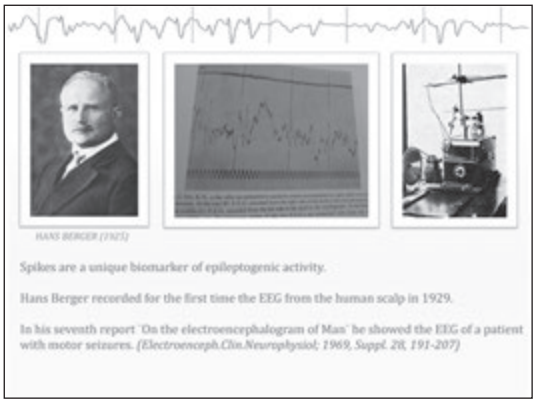
- Conclusion
- FIRES es un síndrome epiléptico severo, bien definido, probablemente en el grupo de las encefalopatías, caracterizado por convulsiones focales o multifocales que se originan de la neocorteza y de etiología aún no determinada.
- El curso evolutivo en nuestra serie de pacientes fue generalmente severo, con convulsiones refractarias a los diferentes esquemas terapéuticos, y asociada con retardo mental y trastornos de conducta.
- Sin embargo, dos de nuestro casos tuvieron buen pronóstico.
- En la fase aguda, el status epilepticus fue controlado con altas dosis de fenobarbital en 5 pacientes. La dieta cetógena fue beneficiosa en 2 pacientes, uno de ellos mantuvo una buena respuesta, y el otro paciente respondió bien a la GGIV. En la fase crónica, fueron consideradas, GGIV, DC, EV y cirugía.

Alicia Bogacz (Uruguay)

WHICH REALLY MATTERS: THE ETIOLOGY OR THE SPIKES?







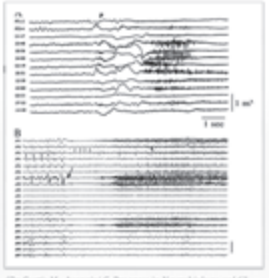
LENNOX, W., 1960 GASTAUT, H., 1974

ATLAS OF EEEG by GIBBS and GIBBS (1952)

The electro-clinical definition of seizures and syndromes of epilepsy since the pioneering works of Lennox and Gastaut has been based, from the EEG findings, on the distribution and frequency of the spikes.

What is the meaning of the spikes?

- Interictal spikes are widely accepted as potentially diagnostic sign of epilepsy, but reasons for the presence of interictal activity in the epileptic brain are controversial.
- The spikes are defined by electrophysiological events and they are not a unique phenomenon. They could be part of the irritative zone or part of the inhibition to control the seizure activity.
- Experimental data indicate that they could play a precipitating or protective role with respect to seizure generation.
- Interictal spikes are easily generated in normal brain by pharmacologically reducing inhibition, and experimental studies of acquired epilepsy indicate that spikes precede seizures *(Chauvière, L. 2012)*.
- Interictal spiking is the first sign of an epileptic discharge appearing after status epilepticus in some animal models *(Staley, K. 2011)*. However, it is unknown whether this activity reflects an altered neuronal network unable to impede the ongoing epileptogenic process or a sign of incipient seizure activity.

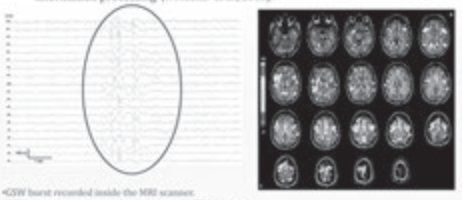


(De Curtis,M., Avanzini,G, Progress in Neurobiology, vol.63, April 2001, 541-567)

Human pre-surgical studies and recordings in chronic and acute models of focal epilepsy, may suggest that:

- Interictal spikes (IS) and ictal discharges may be generated by different populations of neurons through different cellular and network mechanisms.
- The cortical region that generates IS may not always coincide with the *ictal-onset area*.
- IS frequency may not increase before a seizure and it may be enhanced just after an ictal event.
- Spike suppression may herald ictal discharges.
- Enhancement of interictal spiking may suppresses ictal events.

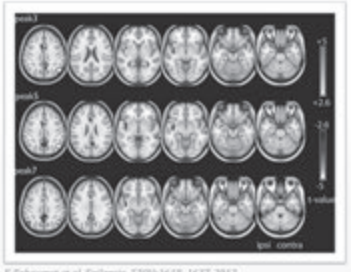
- EEG-fMRI studies have shown the involvement of neural networks in spike and wave discharges in generalized epilepsy.
- There is a network of cortical and subcortical activation and deactivation changes during the discharges. These areas are necessary for normal attention and primary information processing *(F. Moeller et al., 2010)*.



•GSW burst recorded inside the MRI scanner.
•fMRI results superimposed on anatomical MRI showing diffuse cortical fMRI activation, as well as thalamic activation (*Iglseder, F. Brain (2004) 127 (5): 1127-1144.*)

What are the consequences of spikes?

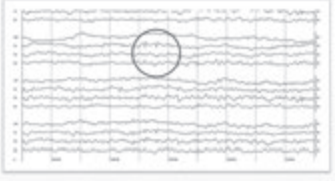
- Even if the spikes are defined as interictal, the cognitive consequences, immediate or in the long term, are established in some syndromes.
- Studies performed in animals suggest that epileptiform discharges can impair cognitive abilities through interference with awake learning and memory, as well as memory consolidation during sleep *(Holmes & Lenck-Santini, 2006; Shatskikh et al, 2006;Zhou et al., 2007).*
- The effects appear to be more pronounced if the spikes are very frequent and widespread.
- Recent studies with EEG-fMRI have found that even if the interictal discharges in scalp EEG are focal, the metabolic changes are widespread *(F. Fahoumet al. 2012).*



F. Fahoumet et al. Epilepsia, 53(9):1618–1627, 2012

Temporal lobe interictal discharges showing Activation clusters in the mid–cingulate gyri bilaterally, and in the ipsilateral insula, mesial and lateral temporal regions, and cerebellum. Significant deactivations are found bilaterally in the inferior parietal lobules, posterior cingulate cortex, and precuneus and in the contralateral posterior temporal cortex.

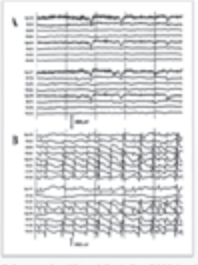
Since Aarts work in 1984, on focal spikes effects in humans, many authors have demonstrated "transitory cognitive impairment" during interictal activity, using simple and complex tasks.



In **Benign childhood epilepsy with centrotemporal spikes (BCECTS), or Benign Rolandic epilepsy,** many studies have shown transient cognitive deficits and learning disabilities *(Deonna, 2000; Deonna et al., 2000; Baglietto et al., 2001).*

These neuropsychological impairments are correlated with some EEG patterns: high number of spikes in the first hour of sleep, and multiple spike-wave foci *(Massa et al., 2001; Nicolai et al., 2007).*

A more recent study found specific learning disabilities associated with an increase in interictal discharges during sleep in patients with BCECTS *(Piccinelli et al., 2008).*



Galanopoulou AS, et al. Brain Dev. **2000** *Aug;22(5):279-95.*

- **The continuous spike and waves during slow sleep syndrome** (CSWSS) shares with Landau-Kleffner syndrome and other disorders with an electrical status epilepticus in sleep (ESES), the cognitive or behavioral impairment acquired during childhood and the strong activation of interictal epileptiform activity during sleep.
- The relationship between the EEG abnormalities and the cognitive disorders is controversial.
- The implications are that if the EEG abnormalities lead to the language, behavioral, and cognitive regression, then the treatment of these epileptic encephalopathies requires reversal of the ESES pattern on the EEG.

- *Attempts to correlate these deficits with the frequency of clinical seizures and with the discharges in EEG have given different results (Stephani,U, 2006; Nicolai et al., 2012).*
- Long-term outcome correlates with duration of the CSWS and the initial cognitive regression. However, some cognitive impairments persist with different degrees in all the patients studied (Praline,J. 2003; Seegmüller,C et al. 2012).

What is the prognostic value of the spikes?

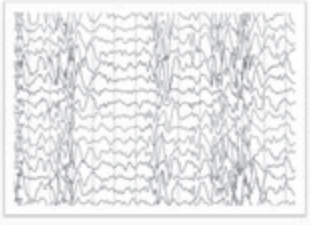
In different clinical situations the presence or absence of interictal activity has a prognostic value from the perspective of seizures recurrence:

- After a single unprovoked seizure, the risk of recurrent seizures in patients with generalized spike-wave discharges in the EEG, increases in a relative ratio of 2.2 *(Annegers, J. 1986; Hauser,1988; van Donselaar, CA et al, 1992).*
- In children, it was found that etiology, EEG, and seizure type were significant predictors of recurrence . An abnormal EEG , especially the presence of spikes, was the most important predictor factor for recurrence in seizures with unknown cause *(Shinnar et al,1990;1996).*
- In complex febrile seizures, Kim,H et al.*(2013)* found that the presence of epileptiform discharges is a significant risk factor for subsequent epilepsy.

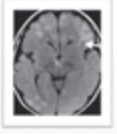
When etiology is known, does the presence of spikes modify the outcome?

In West syndrome, resolution of hypsarrhythmia is considered the key for successful outcomes while its persistence may correlate with cognitive deterioration *(Lux and Osborne, 2004; Gaily et al., 1999; Dulac, 2001).* This beneficial effect of the resolution of hypsarrhythmia is clear only in those infants with no detectable underlying etiology.

However, more than half of infants who develop West syndrome have an underlying neurological disorder *(Koo B, et al,1993).*



Could these underlying etiologies alter the development outcome independent of hypsarrhythmia?



Tuberous sclerosis (TS) is the cause of infantile spasms in 10–20% of patients with West syndrome. Studies of cognitive outcome in these patients showed that both a higher number of cortical tubers and a history of infantile spasms are strongly associated with a lower intelligence level *(O'Callaghan F J K, 2003).*

In a large cohort study of patients with TS , 75% of the patients with a history of infantile spasms were cognitively impaired, compared with 40% without a history of infantile spasms (p <0.0001)*(Chu-Shore C, 2010).*

Infantile spasms occur in up to 13% of patients with Down syndrome. They represent 1% of West syndrome cases(Kurokawa et al., 1980; Strafstrom and Konkol, 1994).

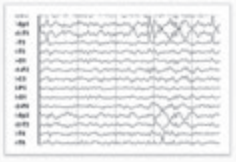
In these patients, all with the same genetic alteration, it was found that a short duration of spasm was associated with high developmental quotient and a lower score of autistic features (Eisermann M, 2003).

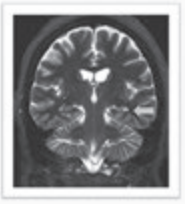
Others found that infantile spasms in Down syndrome are not an independent risk factor for poor cognitive outcomes. They found a higher percentage of autistic features and relapses (Sanmaneechai, O. 2013).

Mesial temporal lobe epilepsy (MTLE) is the most frequent focal epilepsy among adults and is highly associated with hippocampal sclerosis (HS) *(Wieser HG, 2004)*.

HS has been associated with poor medical control of seizures and progresses over time in patients with frequent seizures *(Coan AC, 2009)*.

In refractory mesial temporal lobe epilepsy and unilateral hippocampal atrophy in the MRI, preoperative spike frequency in scalp EEG is a strong predictor for surgical outcome.
In the non frequent spikes group, 80% were seizure free 1 year after surgery whereas only 29% in the frequent spikes group *(Krendl, R. 2008)*.



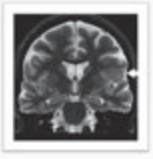


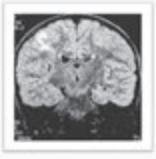
Cortical dysplasia is the most common etiology in children and the third most frequent finding in patients who underwent epilepsy surgery *(Becker et al., 2006; Harvey et al., 2008)*.

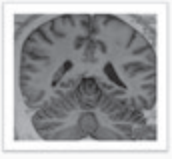
Although early studies found that interictal "continuous epileptiform discharges" (CEDs) on the electrocorticogram were a hallmark of areas of cortical dysplasia *(Palmini et al., 1995; Gambardella et al., 1996; Whiting & Duchowny, 1999)* other studies also found CEDs in different etiologies as well *(Guerreiro et al., 2003; Turkdogan et al., 2005)*.

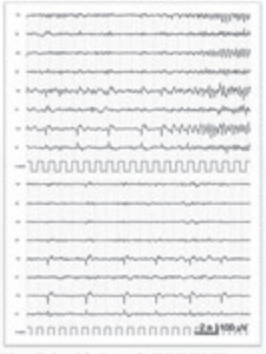
The finding of spikes on the post excision intracranial EEG recording does not predict whether patients will be seizure free after surgery *(Krsek et al., 2008)*.

Studies that summarized the findings from different Epilepsy Surgery Centers concluded that complete resection of the lesion is the only positive predictor of seizure free outcome *(Mathern,G, 2009; Lerner, J. 2009)*.









Even though early papers showed that EEG findings had not prognostic value in traumatic head injury *(Jennett,B. 1974)*, more recent papers found that the risk to have recurrent seizures after a head injury increases 3.5 times in patients with EEG that show focal interictal activity *(Angeleri et al., 1999)*.

In stroke, the presence of electrographic seizures and periodic lateralized epileptiform discharges (PLEDs) are associated with a poor outcome, but not necessarily with recurrent seizures *(Mecarelli et al.2011; Claassen J, 2007)*.

Mecarelli , O. et al. Cerebrovasc Dis 2011;31:191–198

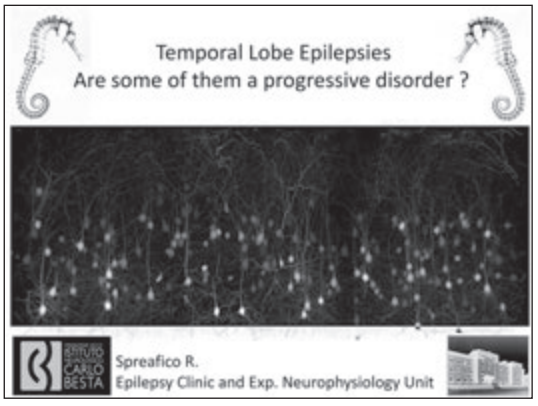
In any case the relation between the etiology and the mechanism of epileptogenesis does not have a direct link and we have a partial understanding of it.

CONCLUSION

If our vision and mission is to cure epilepsy, then our work has to be focused on the integration of the electrophysiological and the etiological findings that are crucial to have a more complete vision of the enduring condition that underlies the seizure activity, which defines epilepsy and allow us the possibility to find a definitive treatment.

Roberto Spreafico (Italy)

DOES SOME MTLE REPRESENT A PROGRESSIVE DEGENERATIVE DISORDER?



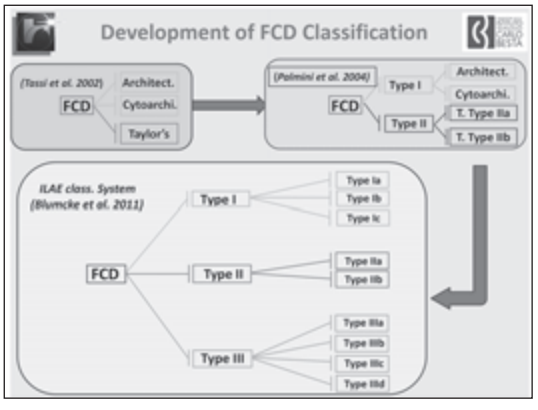
European Epilepsy Brain Bank (EEBB)

Table 1: Neuropathologic categories of symptomatic human epilepsies

Category	Numbers (%)	Age OP	Onset	Duration
HS	1908 (32.7 %)	33.9 + 10.4	11.3 + 7.7	22.7 + 10.0
DUAL	294 (5.0 %)	25.5 + 12.8	9.5 + 7.8	15.9 + 9.9
LEAT	1551 (26.5 %)	27.9 + 12.3	16.5+ 10.1	11.8 + 8.8
MCD	930 (15.9 %)	18.2 + 12.0	5.9 + 5.7	12.3 + 9.1
VASCULAR	328 (5.6 %)	36.1 + 12.3	23.4 + 11.4	12.7 + 9.0
GLIAL SCARS	284 (4.9 %)	25.6 + 12.4	10.3 + 8.0	14.7 + 8.6
ENCEPHALITIS	96 (1.6 %)	20.4 + 12.6	13.3 + 9.4	8.2 + 7.1
NO LESION	451 (7.7 %)	29.2 + 10.8	12.6 + 7.7	16.1 + 8.0
Total	**5842**	**28.6 + 12.5**	**12.4 + 8.9**	**16.5 + 10.1**

Legend to Table 1: Data retrieved from the European Epilepsy Brain Bank. HS: hippocampal sclerosis; DUAL: dual pathologies; LEAT: long-term epilepsy associated tumors; MCD: Malformations of Cortical Development; Age OP = age of patients at surgery (in years); Onset = age at onset of spontaneous seizure activity (in years); Duration = Duration of seizure disorder before surgical treatment (in years).

Courtesy from Prof. I. Blumcke



SPECIAL REPORT

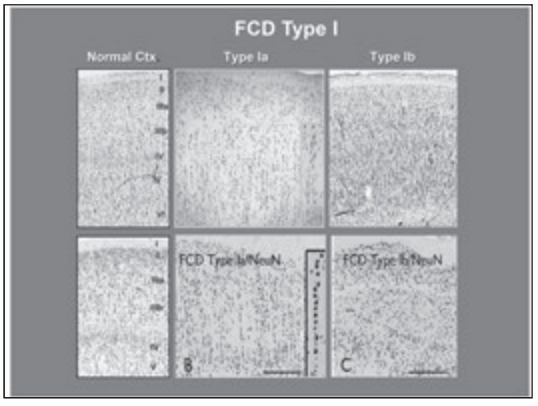
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

*†Ingmar Blümcke, ‡Maria Thom, §Eleonora Aronica, ¶Donna D. Armstrong, #Harry V. Vinters, ∆Andres Palmini, **Thomas S. Jacques, ††Giuliano Avanzini, §§A. James Barkovich, ¶¶Giorgio Battaglia, ##Albert Becker, ***Carlos Cepeda, ***Fernando Cendes, †††Nadia Colombo, §§§Peter Crino, ¶¶¶Helen Cross, ####Olivier Delalande, ∆∆∆François Dubeau, ******John Duncan, †††Renzo Guerrini, §§§Philippe Kahane, §§§Gary Mathern, ¶¶¶Imad Najm, ∆∆∆∆Ceren Özkara, ******Charles Raybaud, §§§§Alfonso Represa, §§§§Steven N. Roper, §§§§Noriko Salamon, ¶¶¶¶¶Andreas Schulze-Bonhage, ∆∆∆∆∆Laura Tassi, ******Annamaria Vezzani, and ††Roberto Spreafico*

Table 1. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

FCD Type I (isolated)	Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)	Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)	Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)
FCD Type II (isolated)	Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)		Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)
FCD Type III (associated with principal lesion)	Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIIb)	Cortical lamination abnormalities adjacent to vascular malformation (FCD Type IIIc)	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis (FCD Type IIId)

FCD Type III (not otherwise specified, NOS): if clinically/radiologically suspected principal lesion is not available for microscopic inspection.
Please note that the rare association between FCD Types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variant.

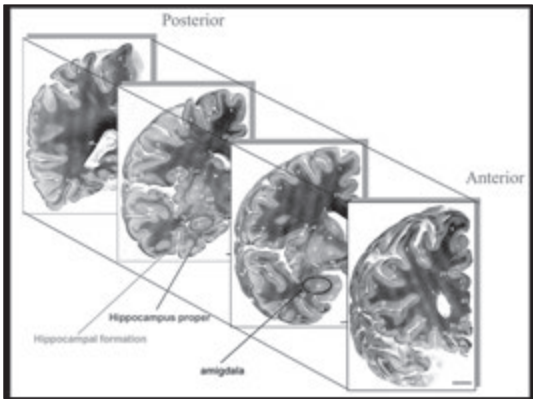


Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and in surgical series of patients with drug-resistant epilepsy, 60-75% of cases are reported to have TLE (Blümcke et al., 2002; Lahl et al., 2003).

However, pathological studies show that lesions correlated with TLE may be found well beyond the hippocampal formation and conventional MRI often identifies developmental or vascular malformations and tumors within the temporal lobe in TLE patients, which may or may not be associated with HS (Kuzniecky et al., 1999; Raymond et al., 1994; Lee et al., 1998).

Dual pathology is estimated to occur in 5-30% of TLE cases.

The most common second alteration is a malformation of cortical development (MCD), including focal cortical dysplasia (FCD) Type II



TERMINOLOGY

Temporal Lobe Epilepsy (TLE) ≠ Mesial Temporal Lobe Epilepsy (**MTLE**)

can be determined by

- different pathologies *(Tumors, HS, Vascular malformations, Focal Dysplasia, etc.)*
- different mesial regions/structures involved (*Hippocampus, Amygdala, Parahippocampal cortex, mesial aspect of the neocortex)*

⇩

Mesial temporal lobe sclerosis (**MTLS**)

Double Pathology

refers to two independent lesions with etiologically defined pathogenesis (neoplastic, infectious, traumatic or metabolic) affecting one or multiple lobes, but not including hippocampal sclerosis

Dual Pathology

Patients with hippocampal sclerosis, who have a second principal lesion affecting the brain (which may be located also outside the ipsilateral temporal lobe), that is, tumor, vascular malformation, glial scar, limbic/Rasmussen encephalitis, or MCD (including FCD Type IIa/IIb).

Of note

histopathologically confirmed architectural abnormalities in the temporal lobe associated with HS should not be diagnosed as FCD Type I or "Dual Pathology" but FCD Type IIIa.

- *Ipsilateral temporopolar atrophy with increased T2 signal changes on MRI is not included as its histopathologic correlate has yet to be specified.*

Blumcke et al. – ILAE classification of FCD – Epilepsia 2011

Neuropathological definitions

HS.....selective neuronal loss + astrogliosis in the hippocampus

HS + FCD I ..... FCD III a

HS + second, distinct principal lesion ..... Dual Pathology

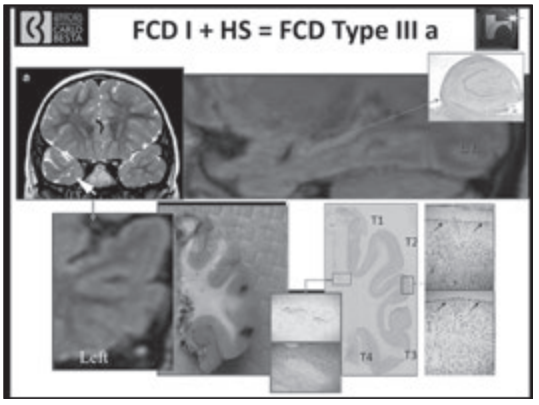
Two independent lesions (other than HS) ..... Double pathology

However recent data suggest different subtypes of temporal epilepsies based on

electroclinical findings

these should not be confused with neuropathological definitions of dual/double pathology

FCD I + HS = FCD Type III a



TLS as a peculiar form of FCD Type IIIa

Architectural (Type IA) Focal Cortical Dysplasia and Parvalbumin Immunostaining in Temporal Lobe Epilepsy

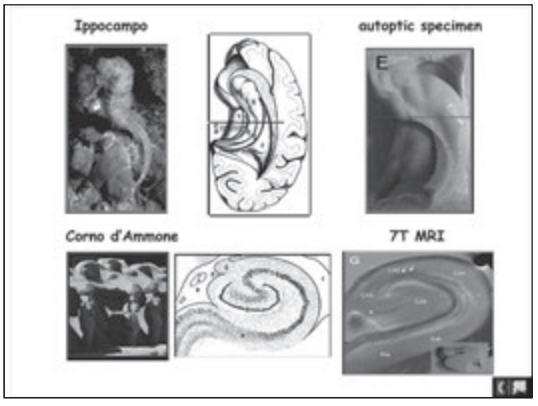
Temporal Lobe Sclerosis Associated with Hippocampal Sclerosis in Temporal Lobe Epilepsy: Neuropathological Features

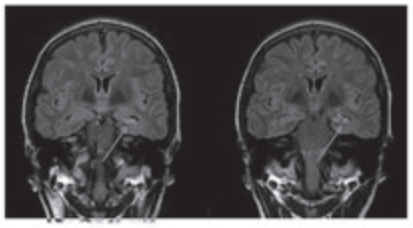
Laminar disorganization

PV decrease

NeuN band in Layer II

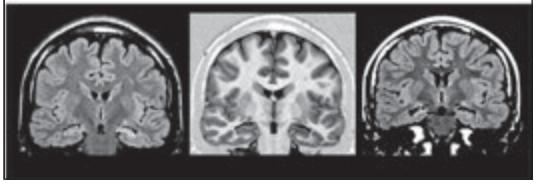
Are some focal cortical dysplasias post-migratory cortical malformations?





MR DIAGNOSIS OF HS

- LOSS OF HIPPOCAMPAL INTERNAL STRUCTURE
- ↓ HIPPOCAMPAL VOLUME
- ↓ SIGNAL IN IR IMAGES
- ↑ SIGNAL IN T2-W.I. AND FLAIR IMAGES



SPECIAL REPORT

International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods

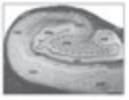
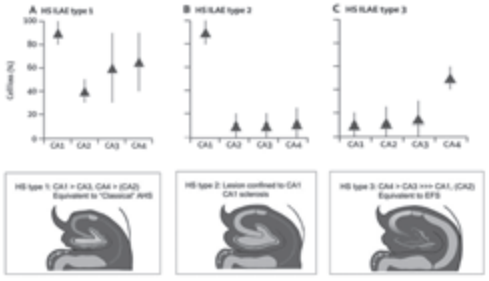


Table 1. ILAE consensus classification of hippocampal sclerosis

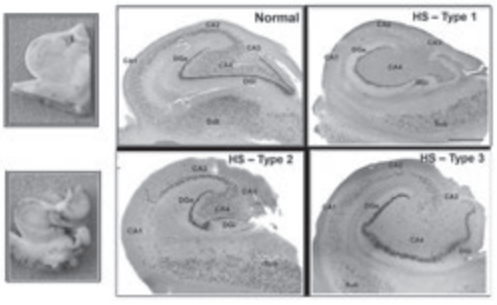
	Subfield pathology patterns of neuronal cell loss and gliosis (in en bloc resected samples)			
Class [a]	HS ILAE Type 1	HS ILAE Type 2 "CA1 Predominant"	HS ILAE Type 3 "CA4 Predominant"	No-HS / Gliosis only
CA1 [b]	2	1 - 2	0 - 1	0
CA2 [b]	0 - 2	0 - 1	0 - 1	0
CA3 [b]	0 - 2	0 - 1	0 - 1	0
CA4 [b]	2	0 - 1	1 - 2	0
DG [b]	0 - 2	0 - 1	0 - 2	0 - 1

New ILAE classification of HS



Miyata et al. Neuropathology 2013

Different subtypes of HS (ILAE Classification)



May 1996 – December 2012
"Claudio Munari" Epilepsy Surgery Centre:

1226 pts operated on

367 pts (30%) with FCD

FCD I: 61 pts

FCD I isolated 61 pts (30%)

FCD III: 124 pts: 4 subgroups

FCD I+ HS	IIIa	74 pts (60%)
FCD I+ tumours	IIIb	39 pts (31%)
FCD I+ vascular	IIIc	2 pt (2%)
FCD I+ "scar"	IIId	9 pts (7%)

Isolated HS 96 pts

Clinical data

FCD I and III: Site of Surgery

	FCD I 61 pts	FCD IIIa + HS 74 pts	FCD IIIb +Tumor 39 pts	FCD IIId +Ischem 9 pts
Temp.	15 (25%)	74 (100%)	33 (85%)	
Front.	20 (33%)		3 (8%)	1 (11%)
Pariet.	1 (1%)		1 (5%)	
Occip.	1 (1%)			
Multilob (-T)	6 (10%)			1 (11%)
Mulitlob (+T)	18 (30%)		2 (2%)	7 (78%)

Clinical data

FCD IIIa and iHS: Outcome

	iHS 95 pts	FCD IIIa + HS 74 pts
Ia+Ic	75 (78%)	54 (73%)
Ib	8 (8%)	4 (5%)
Id	9 (9%)	8 (11%)
Class I	92 (96%)	66 (89%)
II	3 (4%)	2 (3%)
III	0 (0%)	3 (4%)
IV	0 (0%)	3 (4%)

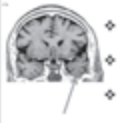
DUAL Pathology

(Blumcke et al – ILAE classification of FCD – Epilepsia 2011)

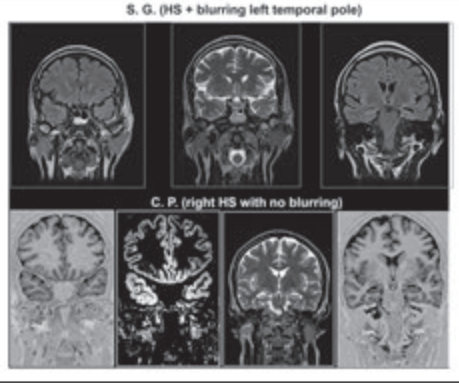
Dual Pathology refers only to patients with hippocampal sclerosis, who have a second, distinct principal lesion affecting the brain.

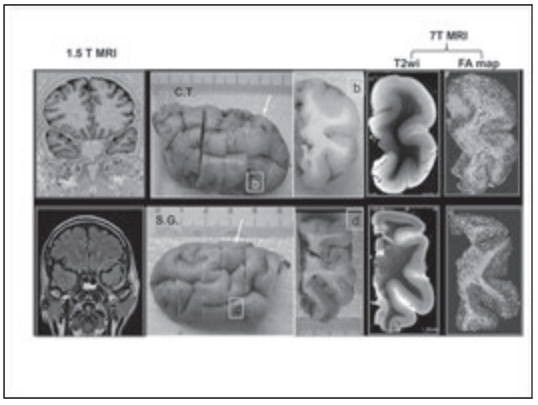
Ipsilateral temporo-polar atrophy with hyperintense signal changes on MRI is not included as its histopathological correlate has to be specified.

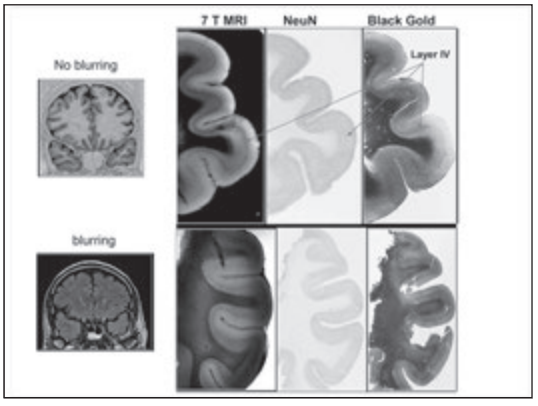
there is no consensus regarding the genesis of temporo-polar abnormalities

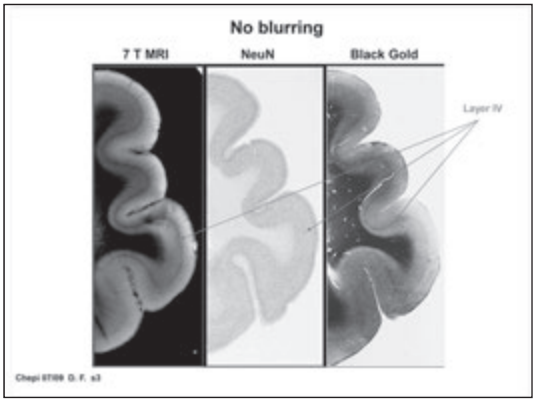


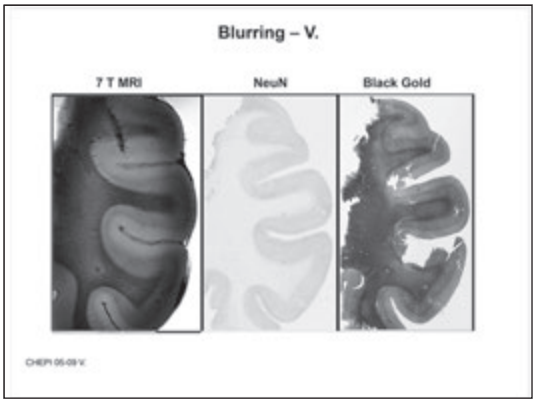
- vascular/metabolic alteration ?
- gliosis ?
- developmental cortical abnormalities (FCD – mMCD) ?
- loss of myelin ?
- non-specific increase in water content ?



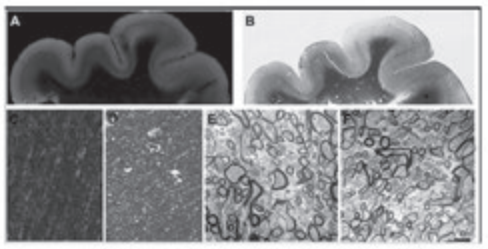

1.5 T MRI
7T MRI
T2wi
FA map
C.T
S.G.


7 T MRI
NeuN
Black Gold
No blurring
Layer IV
blurring

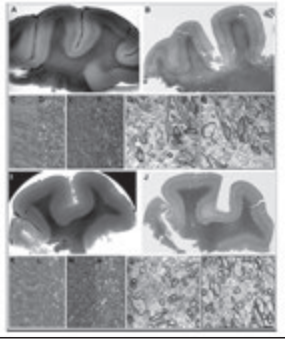

No blurring
7 T MRI
NeuN
Black Gold
Layer IV


Blurring – V.
7 T MRI
NeuN
Black Gold

patient without blurring
Correlative 7 T MRI, histochemical and ultrastructural images

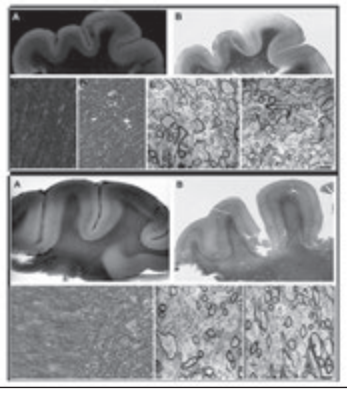


two patients with blurring.
Correlative data from the 7 T MRI, histochemical and ultrastructural images



No blurring

blurring



No blurring

	FS	Age at onset	Age at surgery	Seizure frequency	Duration of epilepsy	Outcome	Cortex	HS
1	si	18	22	8	4	Ia	FCD IA	yes
2	si	10	24	10	14	Ia	FCD IA	yes
3	si	13	45	5	32	Ia	FCD IA*	yes
4	no	11	37	45	26	Ia	FCD IA	yes
5	si	22	27	7	5	Ia	FCD IA	yes
6	si	24	43	3	19	Ia	FCD IB	yes
7	no	14	40	15	26	Ia	FCD IA	yes
8	no	9	34	3	25	II	gliosis	yes
9	si	12	32	4	20	II	FCD IA*	yes
10	no	15	60	15	45	Ia	FCD IA	yes
11	si	10	26	10	16	Ia	FCD IA	yes
12	no	17	42	15	25	Ia	FCD IA	yes
13	si	35	41	1	6	Ia	FCD IA	yes
14	si	8	35	10	28	Ia	FCD IA	yes
15	si	28	34	10	6	Ia	FCD IA*	yes
46,7%		16,4	36,3333	10,73333333	19,6333333	Tot. Class I: 86,7%		
		7,780929067	9,70168	10,80487415	11,7014448			

(FCD IA* indicate patients with TLS according with Thom et al. 2009)

Blurring

	FS	Age at onset	Age at surgery	Seizure frequency	Duration of epilepsy	Outcome	Cortex	HS
1	si	12	33	8	21	Ia	FCD IA	yes
2	no	6	41	4	35	Ia	gliosis	yes
3	no	4	36	4	32	Ib	FCD IA	yes
4	no	8	58	4	50	Ia	FCD IA	yes
5	si	6	45	4	39	Ia	FCD IA	yes
6	si	2	53	3	51	Ia	FCD IA	yes
7	si	8	35	10	27	Ia	FCD IA	yes
8	no	20	31	4	11	II	FCD IA	yes
9	si	6	43	10	37	Ia	FCD IA	yes
10	si	4	32	7	28	Ia	FCD IA	yes
11	si	4	30	15	26	II	FCD IA	yes
12	no	4	43	10	39	Ib	FCD IA	yes
13	si	11	40	7	29	Ia	FCD IA	yes
14	no	4	58	8	54	Ia	FCD IA	yes
15	si	20	28	4	8	II	gliosis	yes
16	no	27	36	3	30	Ia	gliosis	yes
17	si	6	51	7	45	Ib	FCD IA	yes
18	no	3	52	8	49	Ia	FCD IA	yes
19	no	18	35	7	17	Ia	FCD IA	yes
	52,6%	9,105263158	41,05263	6,526315789	34,10526	83,30%		
		7,101601829	9,501308	3,151182414	13,839937			

Table 1 Main clinical characteristics of the patients

History	Blurring	No blurring	Total
History			
Febrile seizure (%)	10 (56)	8 (57)	18 (56)
Mean age at epilepsy onset (SD)	8.6 (7.0)[a]	16.9 (7.9)[b]	12.2 (8.4)
Side of surgery (right-left)	9-9	7-7	16-16
Mean monthly seizure frequency at surgery (SD)	6 (6.4)	10.9 (9.6)	8.1 (8.2)
Mean age at surgery (SD)	41.4 (9.7)	38.0 (8.7)	39.9 (9.3)
Mean duration of epilepsy (SD)	35.1 (13.6)[c]	21.1 (11.2)[d]	29.0 (14.3)
Class I after surgery (%)	15 (83)	14 (100)	29 (91)
Seizure semiology and video-EEG			
Convulsive seizures (%)	4 (22)	7 (50)	11 (34)
Morphic seizures (%)	7 (39)	9 (64)	16 (50)
Fallings (%)	3 (17)	4 (29)	7 (22)
Verbal alert (%)	15 (83)	12 (86)	27 (84)
Ónsolmentary automotions (%)	15 (83)	12 (86)	27 (84)
Manual automotions (%)	16 (89)	10 (71)	26 (81)
Bipedal automotions (%)	3 (17)	1 (7)	4 (13)
Contralateral dystonia (%)	16 (89)[c]	5 (36)[d]	21 (66)
Ómolateral head turning (%)	9 (50)	5 (36)	14 (44)
Awareness of the seizure (%)	18 (100)	12 (86)	30 (94)
Localized interictal abnormalities (%)	17 (94)	12 (86)	27 (84)
Contralateral interictal abnormalities (%)	3 (17)	2 (14)	5 (16)
Localized ictal EEG (%)	15 (83)	10 (71)	25 (78)
Low-voltage fast activity (%)	8 (44)	7 (50)	15 (47)
Mesial temporal seizure pattern (%)	16 (89)	13 (93)	29 (91)
Neocortical temporal seizure pattern (%)	2 (11)	2 (14)	4 (13)
Contralateral diffusion of ictal activity (%)	8 (44)	6 (43)	14 (44)

a versus b = $P < 0.01$.
c versus d = $P < 0.05$.

Statistical test (t-test)

Age at epilepsy onset : p = 0.006
Duration of epilepsy : p = 0.003
Febrile seizures : p = 0.557
Age at surgery : p = 0.166
Seizures frequency : p = 0.078
Short-term surgical outcome : p = 1

Conclusions

1. **The blurring detected by MRI is the result of fibers degeneration and to a consequent increases in water content**
2. **This alteration is dependent from the age at epilepsy onset and duration of epilepsy**
3. **The presence/absence of blurring do not predict short-term surgical outcome**

Questions

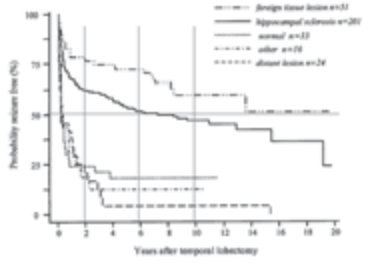
1. Are some bundle of fibers more vulnerable than others and which bundles are more affected?
2. The presence of this neuropathologic/imaging sign is predictive of some other clinical event such as long term relapsing of seizures ?

DOI: 10.1093/brain/awh251 Brain (2004), 127, 2018–2030

Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence

Anne M. McIntosh,[1,2,3] Renate M. Kalnins,[2] L. Anne Mitchell,[3,4] Gavin C. A. Fabinyi,[3] Regula S. Briellmann[3,5] and Samuel F. Berkovic[1,2,3]

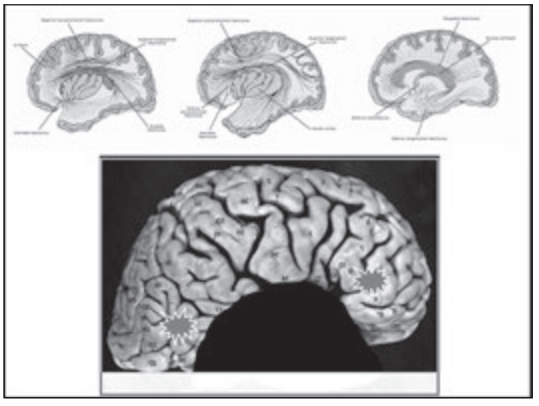
Long-term seizure freedom according to 'best evidence' preoperative pathology



Outcome predictors for surgical treatment of temporal lobe epilepsy with Hippocampal Sclerosis

(*S. Aull-Watschinger et al . Epilepsia 49 (2008): 1308-1316)*

- **Short term surgical outcome of patients remain stable between 70% to 79%**
- **However if** absolute freedom from seizures and auras **is considered, surgical outcome drops down from 65% after 1 year to 46% after 5 years**
- **Positive predictors of short-term outcome do not predict long-term outcome**



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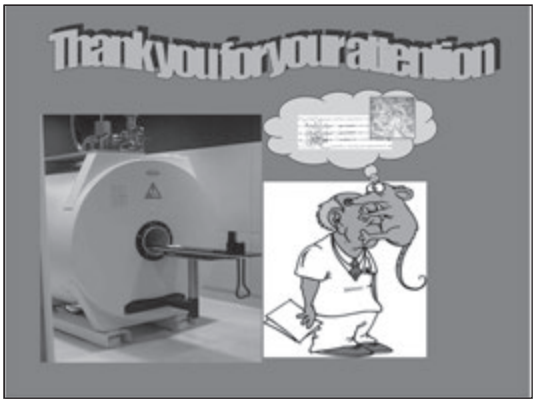
ISTITUTO CARLO BESTA

Clinical Epilepsy and Experimental Neurophysiology Unit *



Jaderson Costa da Costa (Brazil)

ALADE CONFERENCE: NEURODEGENERATIVE DISEASES: THE LOOK OF A PEDIATRIC NEUROLOGIST

Marina Bentivoglio (Italy)

THE STRULDBRUGGS AND NEURODEGENERATION

Giuseppe Bertini (Italy)

WHAT DO WE KNOW ABOUT THE NEUROBIOLOGY OF COGNITIVE DECLINE IN NORMAL "AGING" AND IN NEURODEGENERATIVE DISEASES?

Marina Bentivoglio (Italy)

BRAIN AGING AND NEUROPLASTICITY

Bruce Hermann (USA)

COGNITIVE AND BRAIN CHANGES IN ASYMPTOMATIC PERSONS AT INCREASED RISK FOR ALZHEIMER'S DISEASE

Cognitive and brain changes in asymptomatic persons at increased risk for Alzheimer's disease

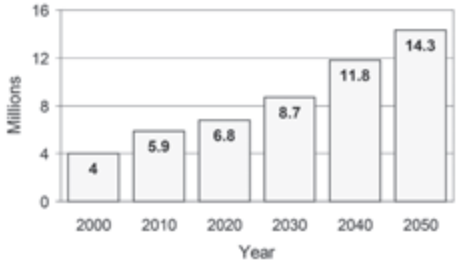
Bruce Hermann, PhD
University of Wisconsin-Madison

Mark Sager, PhD
Sterling Johnson, PhD
Asenath LaRue, PhD
Barbara Bendlin, PhD
Ozioma Okonkwo, PhD
Sanjay Asthana, MD

Alzheimer's Disease: Facts and Figures

- Prevalence
- Cost (direct and indirect)
- Caregiving
- Other

Projected Americans with AD



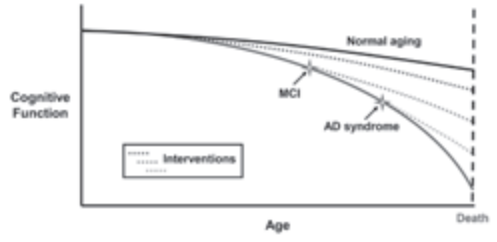
Preclinical Disease

Importance

Definition

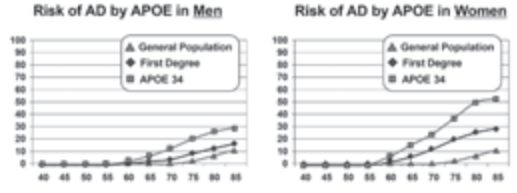
Identification

Course



Importance of Lowering the Risk of Alzheimer's Disease

- Delaying the onset of AD by 10 years would translate into 3.5 million, instead of the predicted 14.3 million, cases over 50 years
- A 2-year delay would translate into 2 million fewer cases over 50 years



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Study of Preclinical AD in a Family History Cohort

Disadvantage

- Absence of a defining biomarker

Advantage

- Dedication to prevention research
- Increased risk of developing AD

Wisconsin Registry for Alzheimer's Prevention (WRAP)

Objective 1: Identify and characterize a group of persons at increased risk of developing AD

Objective 2: Conduct a longitudinal cohort study to define the biological and neurocognitive course of preclinical AD

Wisconsin Registry for Alzheimer's Prevention (WRAP)

- Enrollment: 1094 family history and 421 non family history
- Extensive baseline neuropsychological testing.
- APOE genotyping and laboratory tests for folate, vitamin B12, homocysteine, insulin, glucose, cholesterol, vitamin D, IL-6, hs CRP
- Archived serum, plasma and DNA.

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WRAP Volunteer Characteristics

Mean age	53 years
Gender	71% female
Mean Ed	16 years
Ethnicity	92% non-Hispanic white

Wisconsin Registry for Alzheimer's Prevention (WRAP)

27 states as of 4/2010

Wisconsin Registry For Alzheimer's Prevention (WRAP)

62 counties as of 4/2010

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WRAP Baseline Neuropsychological Test Battery

Domain
Intelligence
Language and verbal ability
Visual spatial
Learning and memory
Executive function and working memory

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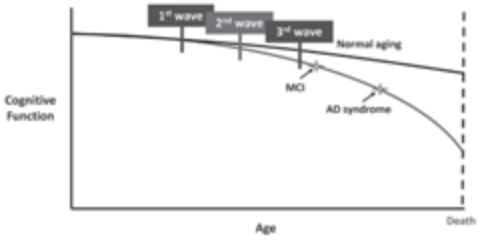
Lifestyle and Environmental Data

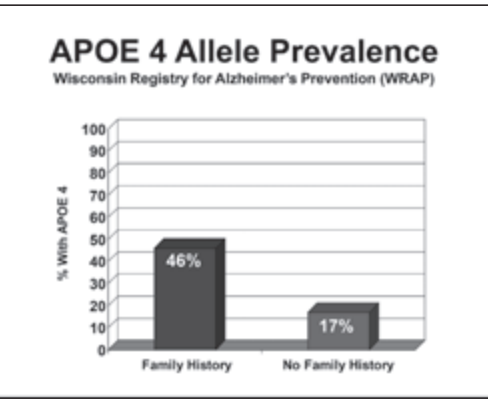
- Education and occupation
- Alcohol/ nicotine consumption
- Psychological stress
- Cognitive and leisure activities
- Physical exercise
- Obesity (BMI and waist hip), diet

Imaging

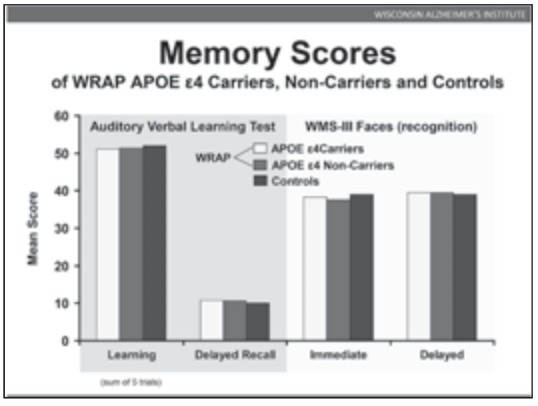
- MRI (FreeSurfer)
- PET (FDG andPiB)
- DTI
- Diffusion
- fMRI

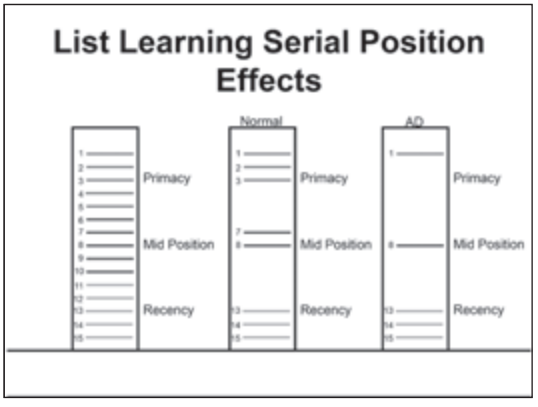


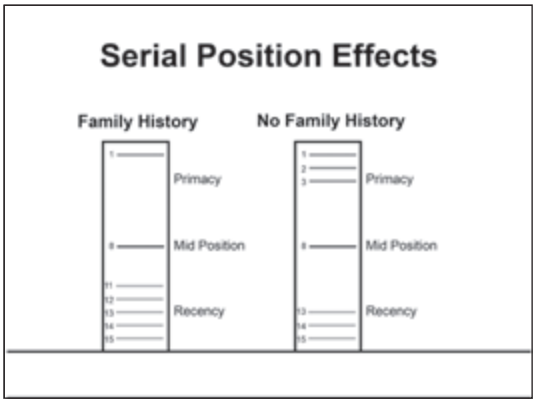
Results




Verbal Ability
Visuo-Spatial Ability
Working Memory
Verbal Learning & Memory
Speed & Flexibility


WISCONSIN ALZHEIMER'S INSTITUTE
Memory Scores
of WRAP APOE ε4 Carriers, Non-Carriers and Controls
Auditory Verbal Learning Test
WMS-III Faces (recognition)
WRAP
APOE ε4Carriers
APOE ε4 Non-Carriers
Controls
Mean Score
60
50
40
30
20
10
0
Learning
Delayed Recall
Immediate
Delayed
(sum of 5 trials)


List Learning Serial Position Effects
Normal
AD
Primacy
Mid Position
Recency


Serial Position Effects
Family History
No Family History
Primacy
Mid Position
Recency

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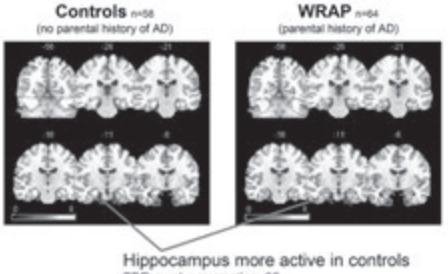
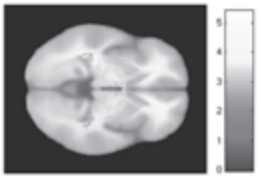
Brain Areas Responding to Novel Items



Hippocampus more active in controls
FDR p-value correction .05

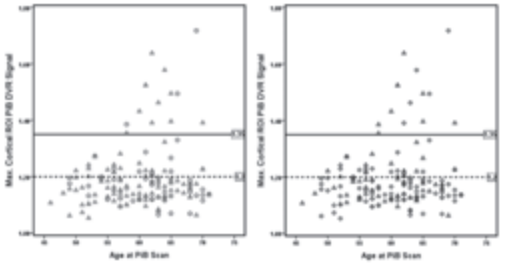
FH+ Show Decreased Hippocampal Fractional Anisotropy vs. FH- Independent of APOE



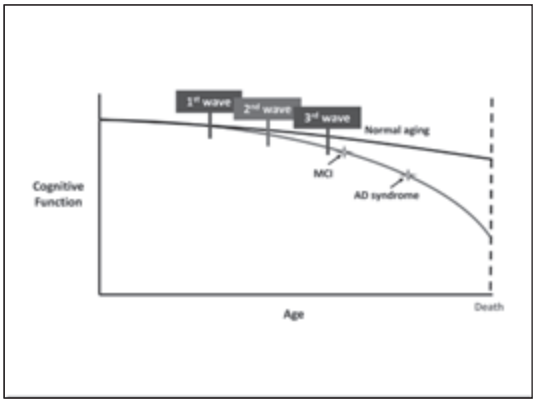
MAIN EFFECT OF FAMILY HISTORY

Independent and/or APOE Interaction Effect of Family History

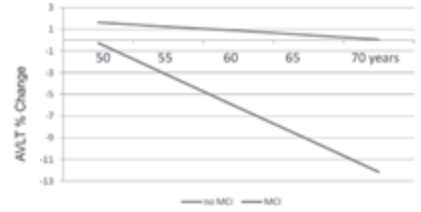
Biomarker	Citation
Brain function	Trivedi, BMC 2006 Johnson, J Neurosurg 2006 Basset, Brain 2006
Brain structure	Donix, Am J Psych 2010 Lunetta, Alz Dis Assoc Dis 2007
Glucose metabolism	Mosconi, PNAS 2007 Mosconi, Neurol 2009
Cognition	La Rue, Alz Dem 2008 Seedenberg, Neurol 2009 Debette, Neurol 2009
Plasma amyloid beta	Ertetan-Tanner, Neurol 2008
Plasma Apolipoprotein E	van Vliet, Neurol 2009

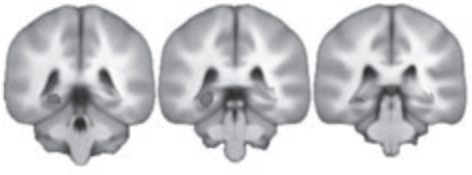


Maximum PiB DVR values in the cerebral cortex. Left: Layered by FH status (red triangle=FH+, blue circle=FH-). Right: Layered by APOE4 status (purple triangle=APOE4+, green diamond=APOE4-).



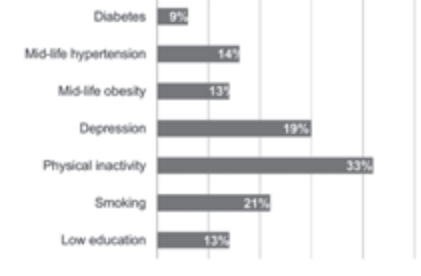
Cognitive Decline in Middle Age



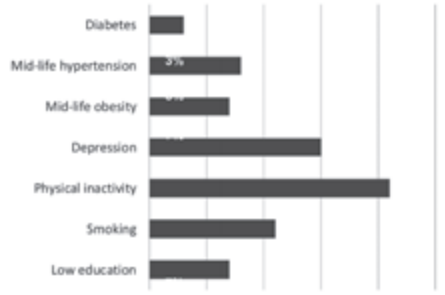


Okonkwo et al *Neurology* 2012. Longitudinal analysis of gray matter change in WRAP (n=108) indicates a significant posterior hippocampal main effect of FH (RED) and APOE4*FH interaction (BLUE).

Modifiable Risk Factors for AD-Prevalence



Population Attributable Risk



Insulin in the Brain

- Increases glucose metabolism and blood flow
- Increases synapse generation
- Protects against beta-amyloid toxicity
- Enhances memory

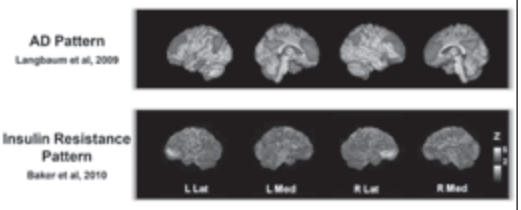
Insulin Resistance

- **Definition:** Cells in body and brain no longer respond to normal amounts of insulin
- **Causes:** Diet, physical inactivity, hypertension, obesity, chronic stress, type 2 diabetes and prediabetes
- **Results in** hyperglycemia, inflammation, vascular dysfunction, dyslipidemia and possibly dementia
- 50% of AD patients are insulin resistant

Effects of Peripheral Insulin Resistance on the Brain

- Reduced glucose metabolism in brain
- Reduced CSF insulin levels
- Decreased beta-amyloid clearance
- Impaired memory

Brain Signature of AD



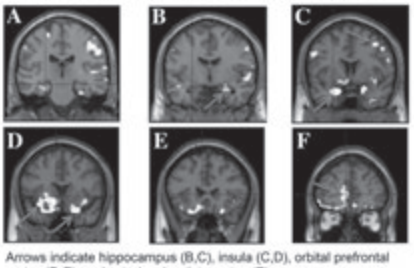
Insulin-resistant older adults with pre-diabetes or newly diagnosed diabetes showed pattern of reduced brain metabolism similar to early AD

Craft 2013, Wake Forest School of Medicine

Effects of Insulin Resistance on Brain in Middle Age

- N=372, mean age 57, 70% women
- Body Mass Index, mean 27.6
- Homeostatic Measurement Assessment of Insulin Resistance (HOMA-IR), mean 2.15
- Type 2 DM, n =7
- Prediabetes, n =95 (25%)
- APOE 4, n= 135 (36%)

Insulin Resistance and Brain Atrophy in Middle Age



Arrows indicate hippocampus (B,C), insula (C,D), orbital prefrontal cortex (D-F), and anterior cingulate cortex (F).

Source: Willette, 2013

Longitudinal Effects of IR on Brain in Middle Age

- Longitudinal data in 121 participants after 4 years
- Higher IR predicted less gray matter in medial temporal, prefrontal cortices and precuneus
- Temporal lobe atrophy predicted worse performance in episodic memory Rey's AVLT

Insulin Resistance and Amyloid Deposition

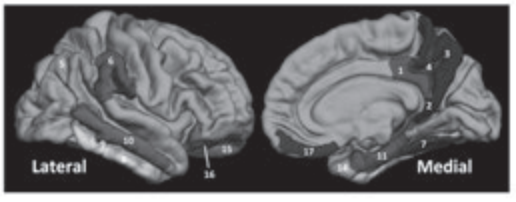
- Wisconsin Registry for Alzheimer's Prevention (WRAP)
- ^{11}C PiB-PET
- Homeostatic Measurement Assessment of Insulin Resistance (HOMA-IR)
- N=176, mean age 61
- Type 2 DM (>125 mg/dL) = 2
- Pre-diabetes (100-125 mg/dL) = 39

Willette 2013

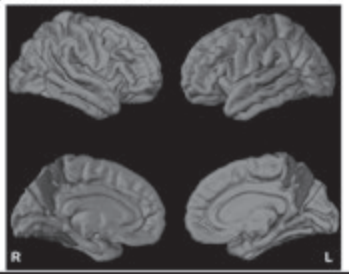
Insulin Resistance and Amyloid Deposition in Middle Age

	Low HOMA-IR (N=108)	High HOMA-IR (>2) N=65
Age $\bar{x}$	60	61
Female (%)	76	49
Family history AD (%)	70	72
APOE4 (%)	39	38
BMI (kg/m^2)	27	31
HOMA-IR ($\bar{x}$)	1.24	3.86

Regions of Interest



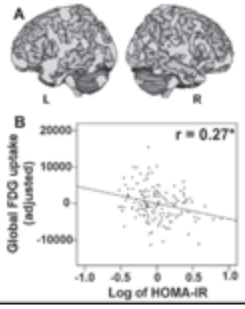
Regions Where Insulin Resistance is Associated with Amyloid Burden



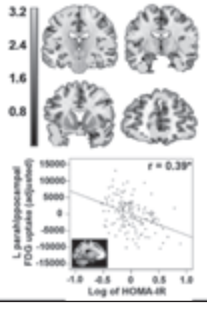
Insulin Resistance and Glucose Metabolism

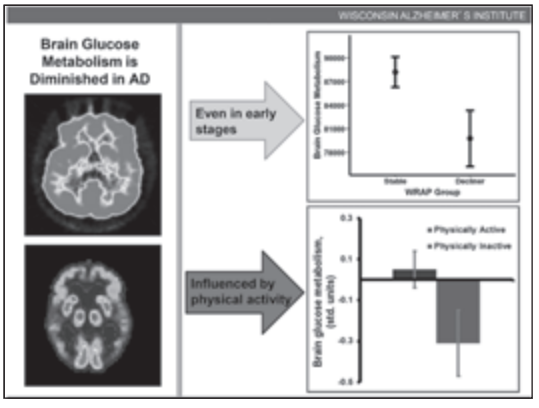
	M ± SD	range
Age	60.7 ± 5.8	47.8 - 71.3
Insulin	2.0 ± 7.0	2 - 48
Glucose	94.6 ± 10.0	74 - 132
HOMA-IR	2.2 ± 1.9	0.5 - 14.1
Speed & Flexibility	28.2 ± 5.3	18.5 - 47.26
Working Memory	0.1 ± 0.9	-2.2 - 2.39
Verbal Learning	0.2 ± 1.1	-2.4 - 3.2
Immediate Memory	0.2 ± 1.0	-2.5 - 1.8
	n (%)	
Female	108 (72.0%)	
Fam His	103 (68.7%)	
APOE4	61 (40.7%)	
Diabetes	7 (4.7%)	

Insulin Resistance and FDG-PET



Insulin Resistance and FDG PET





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Metabolic Syndrome

- 34% of middle aged US adults have metabolic syndrome
- 3 or more factors (abdominal obesity, elevated triglycerides, low HDL, hypertension, elevated fasting glucose)

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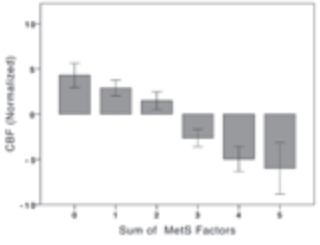
Metabolic Syndrome and Cerebral Blood Flow in Middle Age

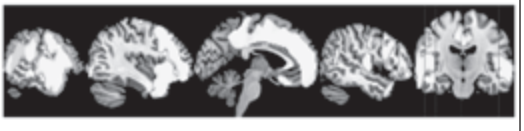
- WRAP
- N=69, Mean age 60 years
- ASL MRI
- Abdominal obesity in men (>102 cm) in women (>88 cm), triglycerides >150, HDL < 40 in men <50 in women, glucose >100, BP > 130/85
- 29 (42%) had metabolic syndrome (exceeded cutoff criteria in 3 or more factors

Cerebral Blood Flow and Metabolic Syndrome

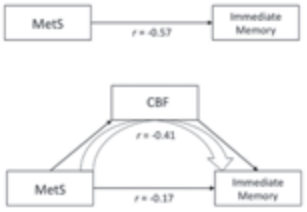


Mean CBF is displayed by groups defined by the number of MetS factors present in an individual. CBF is normalized by a reference cluster and inversion time. Birdsill 2013

CBF in Metabolic Syndrome

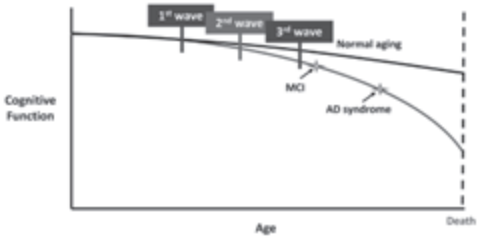


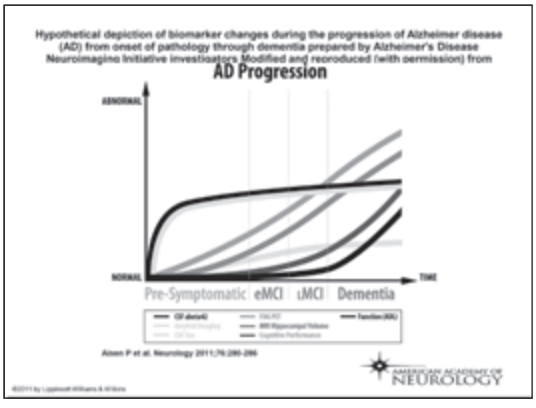
WRAP participants with metabolic syndrome showed significantly lower CBF in large portions of the cortical surface of the frontal and parietal lobes, and the lateral and superior portions of the temporal and occipital lobes. Voxel-wise results are shown here at $p < 0.05$, FWE corrected. The color of the overlay reflects the size of the t-statistic. N=69, mean age 60



Summary

- Insulin resistance affects brain structure and function in middle age
- Insulin resistance is increasing in prevalence
- Normalizing insulin function through diet, exercise and/or medication in midlife may slow the progression or delay the onset of AD





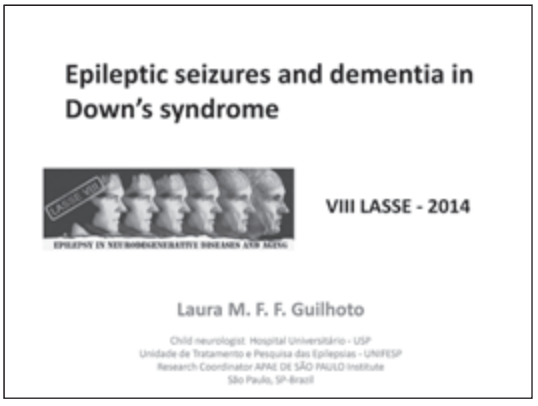
Other Potential Factors

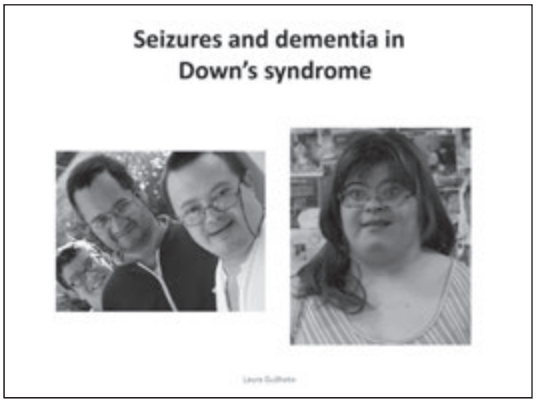
- Socialization
- Mental Activity
- Exercise

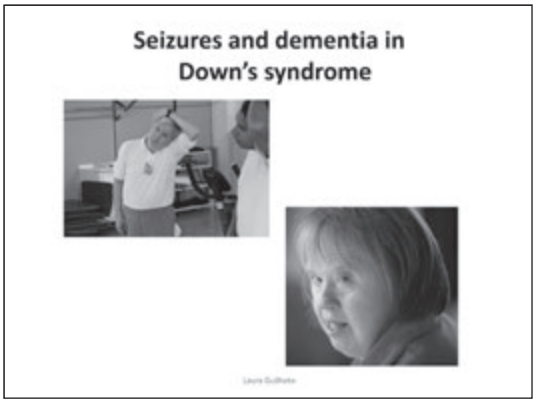
Aging in Epilepsy???

Laura Guilhoto (Brazil)

SEIZURES AND DEMENTIA IN DOWN'S SYNDROME







Seizures and dementia in Down's syndrome

1. History
2. Down syndrome
3. Down syndrome and aging
4. Down syndrome and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

Laura Gulhotta

Seizures and dementia in Down's syndrome

1. **History**
2. Down syndrome
3. Down syndrome and aging
4. Down syndrome and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

Laura Gulhotta

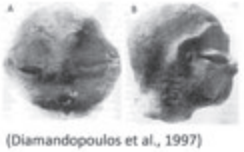
History: Down syndrome

- Descriptions with possible allusions to the physical characteristics of Down syndrome in old objects (pre and post Christianity)
  - Ancient Greece
  - Pre-Colombian America
  - Europe: middle age and Renascence

Laura Gulhotta

History: Down syndrome

Neolithic idol - Greece - 5.000 b.C.



(Diamandopoulos et al., 1997)

(*apud* Starbuck, 2011)

Egyptian figure - 100 A.D.

(Kunze & Nippert, 1996)

Laura Gulhotta

History: Down syndrome

– Olmec figures - Meso-America 1500 b.C.
(Milton & Gonzalo, 1974)

(*apud* Starbuck, 2011)

History: Down syndrome

- Peru – 1.200-1.500 b.C.
(Wells, 1964; Ebbin et al., 1968)

(*apud* Starbuck, 2011)

- Culture Tumaco-La Tolita - Colombia and Ecuador – c. 500 b.C.
(Bernal & Brecino, 2006)

History: Down syndrome

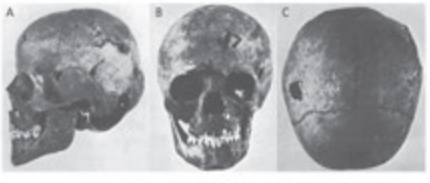
- Monte Alban – Mexico - 400-800 A.D.
(Kunze & Nippert , 1986)

(*apud* Starbuck, 2011)

- Terracotta figure – culture Tolteca - Mexico – c. 500 A.D.
(Martinez-Frias, 2005)

History: Down syndrome

- Breedon-on-the-Hill – England (700-900 A.D.)
(Brothwell, 1960)



(*apud* Starbuck, 2011)

History: Down syndrome



(*apud* Starbuck, 2011)

The Adoration of the Christ Child
Jan Joest of Kalkar (Netherland, c. 1515)

Laura Guilhoto

History: Down syndrome

Lady Cockburn and her children
Joshua Reynolds (1723-1792)


The Adoration of the Shepherd
Jacob Jordaens (1593-1678) (c. 1618 A.D.)


(*apud* Starbuck, 2011)

Laura Guilhoto

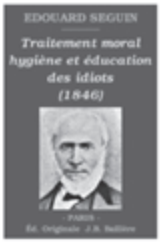
History: Down syndrome

- First clinical descriptions are considered those done in 1838 by French Psychiatry Jean-Étienne Dominique Esquirol
  - Difference: mental disease X mental deficiency


Laura Guilhoto

History: Down syndrome

- French physician Onésime-Édouard Séguin
  - 1846: publication of first treaty of education in children with intellectual disability
  - description of some features found in Down syndrome



Laura Guilhoto

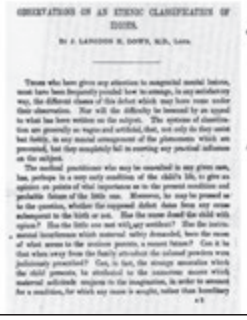
History: Down syndrome

- 1866 English physician Longdon Down, contemporaneously to Mendelian laws discovery, described in details the features of the children called mongoloids, how were named the people with Down syndrome

—[…] when placed side by side, it is difficult to believe that the specimens compared are not children of the same parents. (Down, 1866).

Laura Guilhota

History: Down syndrome



OBSERVATIONS ON AN ETHNIC CLASSIFICATION OF IDIOTS.

By J. LANGDON H. DOWN, M.D., Lond.

- Down JL. Observations on an Ethnic Classification of Idiots. London Hospital Reports, 3:259-262, 1866.

"….The life expectancy, however, is far below the average,……"

Laura Guilhota

History: Down syndrome

- 1959 Jerôme Jean Louis Marie Lejeune, French geneticist, published with his group, after the description of DNA by Watson & Crick in 1953, the genetic abnormality in Down syndrome, the **trisomy of chromosome 21**

Laura Guilhota

History: Down syndrome

- Lejeune J. Le mongolism: premier exemple d'aberration autosomique humaine. Ann. Genet. 1, 41-9 (1959)
- Lejeune J, Turpin R, Gautier M. Chromosomic diagnosis of mongolism. Arch Fr Pediatr. 16:962-3 (1959).

Laura Guilhota

History: Down syndrome

- Terminology:
  - In 1961 the term mongolism was replaced by **trisomyc anomaly of chromosome 21** or **Down syndrome**
  - Down syndrome (USA)
  - Trisomy of chromosome 21 (Europe)

Laura Guilhoto

History: Down syndrome

- In 2012 UNESCO promulgated the International day of Down syndrome celebrated in March 21

http://www.worlddownsyndromeday.org/

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Seizures and dementia in Down's syndrome

1. History
2. **Down syndrome**
3. Down syndrome and aging
4. Down syndrome and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. Conclusions

Laura Guilhoto

Down syndrome

- Down syndrome (DS) : trisomy of chromosome 21
- 1-3/1.000 live births
- Longer life expectancy nowadays, better clinical characterization
  - Early aging
  - Dementia as in Alzheimer disease

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Down syndrome

Most common genetic cause of intellectual disability

- Trisomy 21 (HSA21) (47, +21): 95%
  - ✓ Frequency of trisomy increases with increasing maternal age
- Robertsonian translocation involving chromosome 21: ± 3%, not related to maternal age
- Trisomy 21 mosaicism – 2% cases

Laura Gulhehe

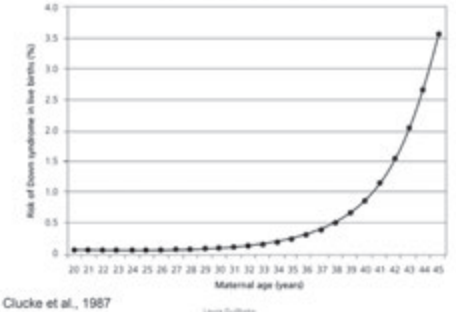
Relationship Of Down Syndrome Incidence To Mothers Age

Hook, E.G., Lindsjo, A. Down Syndrome in Live Births by Single Year Maternal Age (1978)

Mothers Age	Incidence Down Syndrome
Under 30	Less then 1 in 1,000
30	1 in 900
35	1 in 400
36	1 in 300
37	1 in 230
38	1 in 180
39	1 in 135
40	1 in 105
42	1 in 60
44	1 in 35
46	1 in 20
48	1 in 16
49	1 in 12

Laura Gulhehe

Down syndrome



Clucke et al., 1987

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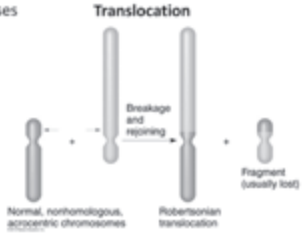
Down syndrome

- 2% of cases



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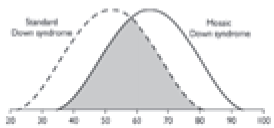
Down syndrome

Trisomy 21 mosaicism – 2% cases



Down syndrome

-40% of known causes of Intellectual Disability
-Related to maternal age during gestation
-Intellectual disability within a spectrum
-Typical facial features
-Abnormalities: cardiac, metabolic (thyroid), orthopedic (ligament laxity), ocular and immunological dysfunction

Down syndrome

- Single phenotype, variable expression and epigenetic influence
- Clinical characteristics
  - Oblique eyelid folds , epicanthus, acromicia, tongue protrusion, brachydactyly, hypotonia, single palmar crease, etc..
- Pre-natal diagnosis (95%)
  - Human chorionic gonadotropin
  - Nuchal translucency
  - Alpha-fetoprotein
  - Amniocentesis
  - Chorionic villus sampling
  - Detection of cells with trisomy in maternal blood

Karyotyping in Down syndrome

Non-disjunction trisomy 21	95%
Robertsonian translocation	3%
[redacted]	

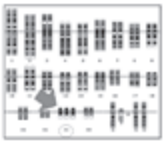
Recurrence risk by karyotype

Non-disjunction trisomy 21	
47(XX or XY) + 21	1%
Translocation	
both parents normal	<1%
[redacted]	
father carrier	3%
[redacted]	
mother carrier	12%
[redacted]	
mosaics	<1%

(Bencke, 1995)

Down syndrome

Normal set of chromosomes



Down syndrome

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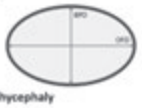
Down syndrome

Brushfield spots (iris)



Brachycephaly

Oblique (up-slanting) eyelid folds

Prominent epicanthus

Folded or dysplastic ears

Flat nasal bridge

Hypoplastic maxilla

Short neck

Small mouth (open)

Tongue protrusion

Excessive skin at nape

(W. Commons, 2013)

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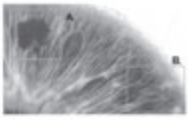
Down syndrome

- Epicanthal folds are prominent

- The iris has the light smudgy opacities of Brishfield spots



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Down syndrome

Extremities

- Short broad hands
- Short fifth finger
- Incurved fifth finger
- Transverse palmer crease
- Space between first and second toe
- Hyper flexibility of joints

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Down syndrome

Dental Anomalies

- Microdontia in 35-55%
- Hypoplasia and hypocalcification are common
- Congenitally missing teeth (partial anodontia) occur in 50% of people with Down syndrome
- Delay in the eruption of dentition

(Desai, 1997)

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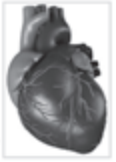
Down syndrome



Newborn

- cardiac defects
- gastrointestinal: duodenal atresia, tracheo-oesophageal fistula, anorectal malformation, pyloric stenosis and Hirshsprung disease
- vision: congenital cataracts, glaucoma
- hypotonia & joint laxity
- feeding problems
- congenital hypothyroidism
- congenital dislocation of the hips

(Hickey et al., 2012; Bull, 2011)

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Down syndrome

Infancy and Childhood

- hypothyroidism (10%) (prev. increases with age)
- short stature
- congenital heart disease
- coeliac disease
- nutritional inadequacy due to feeding problems and thyroid hormone deficiency
- over/underweight
- recurrent respiratory infections
- leukemia (relative risk: 15 to 20 times): incidence 1%

(Hickey et al., 2012; Bull, 2011)

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Down syndrome

Infancy and Childhood

- delayed developmental milestones
- mild to moderate intellectual impairment (IQ 25 to 50)
- epileptic seizures (6%)
- hearing loss (>60%) due to secretory otitis media, sensorineural deafness, or both
- visual impairment – squint (50%), cataract (3%),
- nystagmus (35%), glaucoma, refractive errors (70%)
- sleep related upper airway obstruction

(Hickey et al., 2012; Bull, 2011)

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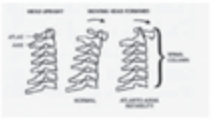
Down syndrome

Infancy and Childhood

- Atlantoaxial instability
  - children with Down syndrome should not be barred from taking part in sporting activities
  - appropriate care of the neck
    - under general anesthesia (Hickey et al., 2012; Bull, 2011)
    - after road traffic accident



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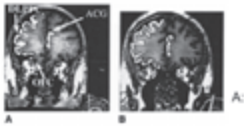
Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates:
Evidence from MRI morphometry



Neurology 1995;45:356-366

A: DS B: control

Down syndrome

Smaller: cerebral and cerebellar hemispheres, pons, mammillary bodies, hippocampal formation, cerebellar vermis: smaller lobules VI- VIII; decreased dorsolateral prefrontal cortex, anterior cingulate gyrus, inferior parietal and temporal cortex, parietal white matter and pericalcarin cortex;

Larger: parahippocampal gyrus

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Down syndrome

- Why the phenotipical spectrum?

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Seizures and dementia in Down's syndrome

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6. Conclusions

Laura Guilhoto

Down syndrome and aging

- Up to 35 yrs. mortality rate similar to other causes of intellectual disability
  - After 35 yrs.: mortality rate doubles each 6.4 yrs. vs each 9.6 yrs. in people without Down syndrome (Strauss & Eyman, 1996; Head et al., 2012)
  - Down syndrome involves the overexpression of amyloid precursor protein in chromosome 21

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Down syndrome and aging

Early aging

- Life expectancy 12 yrs. in 1949 to 60 yrs. in 2010 (Bittles & Glasson, 2004; Penrose, 1949)
- Skin/hair abnormalities
- Early menopause
- Visual and auditory abnormalities
- Late epilepsy
- Thyroid dysfunction
- Diabetes, obesity
- Sleep apnea
- Muscle and skeletal abnormalities

(Esbensen, 2010)

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Down syndrome

Mortality (Esbensen, 2010)

- Life expectancy still below the general population
  - Women with DS: shorter than men (premature menopause?)
- Predictive factors: previous functional abilities, age, worsening of behavior disorders
- Common causes of death: leukemia, respiratory disease, circulatory congenital malformations, dementia
- In children with DS: leukemia (after respiratory problems and congenital heart defects)
- Mortality due to the risk of cancer in adults with DS is equal to or lower than in general population or in other causes of ID
  - In particular, risk of mortality from solid tumors among adults with DS is considerably lower

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Down syndrome - Adult life

- Respiratory problems and birth defects: more common
- Ischemic CV disease: less common
- High frequency of mitral valve prolapse
- Decreased risk for CV and cerebrovascular disease
- Lower frequency of emphysema, fractures, hypercholesterolemia and heart disease compared to adults with ID from other causes
- Lower resting heart rate and lower blood pressure than the general population

(Esbensen, 2010)

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Comparison of Intima-Media Thickness of the Carotid Artery and Cardiovascular Disease Risk Factors in Adults With Versus Without the Down Syndrome

Christopher C. Draheim, PhD[a], Justin R. Gerjes, MS[a], and Donald R. Dengel, PhD[a,b,c]

Adults with DS lower arteriosclerosis levels ?

- CV disease risk: intima-media thickness of carotid artery (IMT)
- Method: B-mode imaging L common carotid
- 52 adults with DS (25 male, mean age 42yrs.) x controls

DS:

- lower levels
  - IMT (0.43±0.07 vs 0.48±0.09 mm, p <0.001)
  - Systolic BP (116±15 vs 125±17 mm Hg, p <0.011)
  - Diastolic BP (59±10 vs 73±9 mm Hg, p <0.001)
- Higher levels
  - Protein C-reactive (0.58±0.55 vs 0.30±0.42 mg/dl, p <0.003)
  - Triglycerides (126.5±55.2 vs 103.8±53.2 mg/dl, p <0.048)
  - Total fat (37.8±10.2% vs 32.4±11.2%, p <0.002)
- Males (p <0.001) and physical activity (p=0.020) predictors of IMT for adults with DS
- Fasting insulin (p <0.001), age (p <0.001), gender (p <0.001), fruit and vegetable intake (p=0.001), LHDL cholesterol (p=0.004), smoking (p=0.023) for controls

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(Drahmeim et al., 2010)

Seizures and dementia in Down's syndrome

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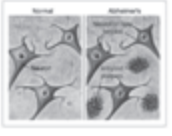
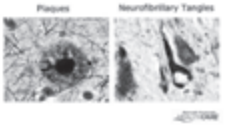
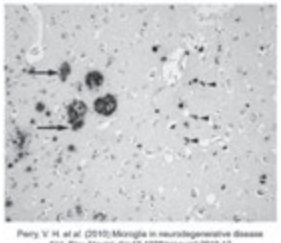
Alzheimer's Disease Plaques and Tangles

- Cause or symptom ?
- Amyloid Plaques are deposits of beta-amyloid protein that build up in the spaces between nerve cells
- Neurofibrillary Tangles are twisted fibres of tau protein that build up inside cells
- Neocortical atrophy with neuronal loss, synaptic loss
- Neurochemical changes – cholinergic deficits to cortical and limbic regions





Aβ immunization in Alzheimer disease induces amyloid plaque phagocytosis by activated microglia



Perry, V. H. et al. (2010) Microglia in neurodegenerative disease. *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2010.17

nature REVIEWS NEUROLOGY

Down syndrome and Alzheimer disease

- Age
- Gender (even when controlling for longevity)
  - Females increased AD likelihood
- Vascular risk factors (smoking, vascular disease, diabetes, etc), even in AD
- Head trauma
- Education? Cognitive reserve
- Family history
- Apolipoprotein E (ApoE) status

(McCullagh et al., 2001)

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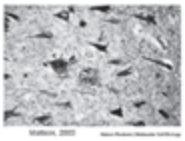
Down syndrome and Alzheimer disease

- Plaques and tangles in the brain tissue present in the brains of nearly all adults with Down syndrome by the age of 40

(Malamud, 1972; Wisniewski et al. 1985)



Wallace, 2003

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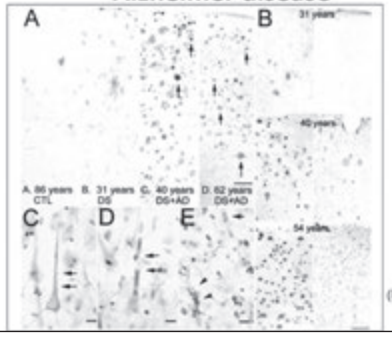
Down syndrome and Alzheimer disease

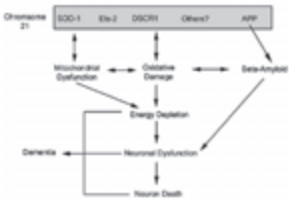


(Head & Lott, 2001)

Down syndrome and Alzheimer disease

- Increased life expectancy
- Link between chromosome 21 and amyloid production
- Average age of onset is 55 yrs.
- 9 years (on average) from diagnosis to death
- Virtually all people with DS >40 years show characteristic brain changes of AD - although not all show clinical signs

Down syndrome and Alzheimer disease



(Lott et al., 2006)

Down syndrome and Alzheimer disease

(Head & Lott, 2004)

Down syndrome and Alzheimer disease

Obesity

– Individuals with Down syndrome are more likely to be overweight or obese than other individuals with intellectual disability (Stancliffe, 2011)

- Intellectual disability & DS – mean BMI 30.40
- Intellectual disability only – mean BMI 28.55
- Intellectual disability & autism/PDD – mean BMI 27.42
- Intellectual disability & CP – mean 24.53

	Obese (BMI ≥ 30)	Overweight or Obese (BMI ≥ 25)
Down syndrome	44.3%	72.7%
U.S. population	33.8%	68.0%

(Flegal et al., 2010)

Down syndrome and Alzheimer disease

Sedentary Lifestyle

- Levels of physical activity in non-athletic adults without intellectual disability were twice as high compared to adults with an intellectual disability (Vis et al., 2011)
- No significant difference between Down syndrome and other causes of intellectual disability

Down syndrome and Alzheimer disease

Alzheimer disease in the general population

- Roughly 10% of people 65 yrs. and older
- Nearly 50% of people 85 yrs. and older

Clinical symptoms of dementia in Down syndrome

- <10% between 30-39 yrs. of age
- 10-25% between 40-49 yrs.
- 20-50% between 50-59 yrs.
- 50-70% by 60-70 yrs.
- Variable, however seems to progress more quickly than in general population

(Mann & Esiri, 1989; Prasher, 1994; Holland et al., 1998)

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Down syndrome and Alzheimer disease

1st symptom is usually behavioral changes

- Disorientation to time/place
- Personality or productivity changes
- Increased apathy or inactivity
- Memory loss may not be first symptom noticed
- Inability to perform activities of daily living
  - Difficulty dressing, bathing, toileting
  - Later on – Difficulty eating
- Personality changes
  - Aggression/spitting/hitting/kicking
  - Irritability
  - Anxiety
  - Depression

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Down syndrome and Alzheimer disease

Differential diagnosis

- Medications
- Pain (headache, neck and back pain, etc.)
- Sleep apnea
  - Other factors affecting sleep
    - Depression
    - Anxiety
    - Pain
    - Environmental factors

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Down syndrome and Alzheimer disease

Compared to younger non-demented with Down syndrome

- More irritation
- Fear
- Restlessness at night
- Sadness
- Suspiciousness
- Loss of appetite

(Haveman et al. 1994)

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Down syndrome and Alzheimer disease

- By Karen Watchman, Diana Kerr and Heather Wilkinson
- University of Edinburgh
- Joseph Rowntree Foundation

http://www.youtube.com/watch?v=O3ekO4QdKXU

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Down syndrome and Alzheimer disease

Main points

- Mild to moderate cognitive deterioration since birth is the hallmark of the condition
- Deposits of beta-amyloid and neurofibrillary tangles from the first years of life
- Increased life expectancy
  - 1949: 12 years
  - Today: 60 years

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Down syndrome and Alzheimer disease

Main points

- Cognitive impairment
  - 39-45 yrs.: 8%
  - After 60 yrs.: 75%
- Chromosome 21 – DS x AD
  - Increase in oxidative stress and inflammation
  - Amyloid protein precursor
- Basal frontal dysfunction, hippocampal, *locus coeruleus*

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Down syndrome and Alzheimer disease

Main points

- Emotional abnormalities
- Verbal regression
- Recent memory impairment
- Spatial organization
- Reduction in cerebral volume (except parahippocampal girus)
- Disturbance in gait and sphincters
- Epilepsy

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Down syndrome and Alzheimer disease

Diagnosis

•Dementia Questionnaire for the Mentally Retarded – **DMR** (Evenhuis, 1988)

•Carer questionnaire, measures cognitive and social functioning across 8 sub-scales, divided into two areas:

- **Cognitive Score**: short and long term memory, spatial and temporal orientation
- **Social Score**: speech, practical skills, mood, activity and interest, behavioural disturbance

•Evenhuis (1992, 1996) reported sensitivity up to 100% in identifying dementia; proposed cut-off & change scores for probable dementia

•Prasher (1997) independent evaluation on 100 adults with DS in UK - poor specificity, suggested modifications to the cut-off scores

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Down syndrome and Alzheimer disease

Diagnosis

- Cambridge Mental Disorders of the Elderly Examination - **CAMDEX** (Roth et al., 1986)
- Section A: structural clinical interview with patient and family
- Section B: cognitive test with 67 items **(CAMCOG),** including Mini-mental exam
- Modified version of CAMCOG for DS

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Seizures and dementia in Down's syndrome

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Down syndrome and epilepsy

- Epilepsy: approximately 5-13%
- Epilepsy incidence

  General Population < DS < ID
- Bimodal pattern
  - Early childhood (infantile spasms, reflex seizures, Lennox-Gastaut syndrome)
  - Adults (focal seizures, tonic-clonic, reflex seizures, late onset myoclonic epilepsy - LOMEDS)
    - 18-35 yrs.
    - >35yrs.

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Down syndrome and epilepsy

Epilepsy Prevalence

>50 yrs. and DS

46% (McVicker et al., 1994)

NON-SD and Alzheimer Disease

10-12% (Bernardi et al., 2009)

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Down syndrome and epilepsy

Putative mechanisms of epileptogenesis in DS

Neuronal or synaptic anatomy
- Fewer inhibitory inter-neurons - Decreased neuronal density - Abnormal neuronal lamination - Persistence of dendrites with foetal morphology - Primitive synaptic profiles
Membrane channel dysfunction - Altered membrane potassium permeability - Decreased voltage threshold for spike generation - Smaller hyperpolarization following spikes - Altered action potential duration

(Stafstrom, 1993; Stafstrom et al., 1991; Arya et al., 2011)

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Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)

- Pedersen, 1990: first report of myoclonic seizures in adults with DS
- Genton & Paglia, 1994: 2 patients with LOMEDS
  - Beginning after the 4th decade of life
  - Myoclonic seizures on awakening and generalized tonic-clonic seizures
- EEG: generalized discharges of spike-wave complexes
- Clinical picture similar to juvenile myoclonic epilepsy
- Myoclonic seizures usually unnoticed
- Diagnosis of importance: evolution to convulsive seizures and falls: ⟹ worse prognosis

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Epilepsie myoclonique sénile ?
Myoclonies épileptiques d'apparition tardive dans le syndrome de Down

Pierre Genton*, Gabriella Paglia*

Epilepsie myoclonique sénile

1994

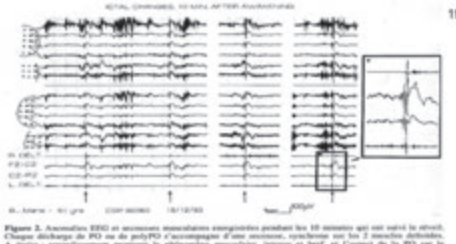
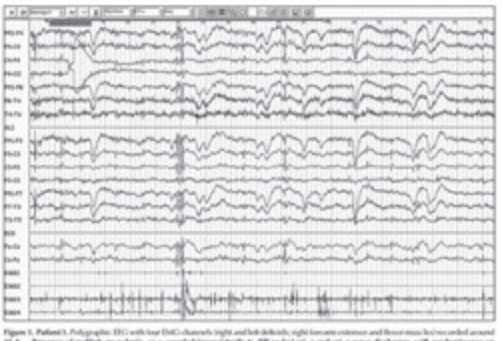
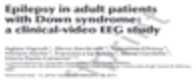


Figure 2. Anomalies EEG et accusés musculaires enregistrées pendant les 10 minutes qui ont suivi le réveil. Chaque décharge de PO ou de poly/PO s'accompagne d'une secousse, synchrone sur les 2 muscles délteides. A droite : agrandissement montrant le phénomène musculaire, intense et bref, et l'aspect de la PO sur le vertex, où son amplitude est maximale.



(Genton & Paglia, 1994)

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)



Epilepsy in adult patients with Down syndrome: a clinical-video EEG study

Vignoli et al., 2011

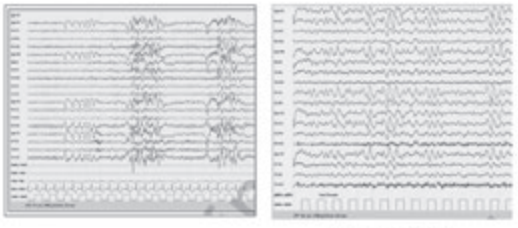
22 patients with epilepsy and Down syndrome

- mean age: 46 yrs.
- onset of epilepsy: 36.8 yrs.
- 9 patients – focal seizures
- **9 patients – LOMEDS**
- 4 patients – non classified

LOMEDS

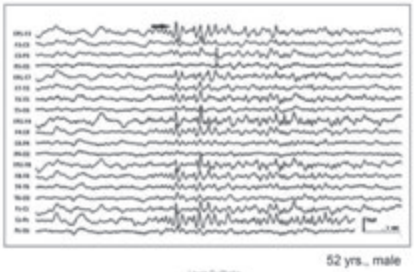
- Mean age at epilepsy onset: 50.2 yrs.
- Cognitive decline preceded any obvious seizure 6-18 months (5/9) or occurred at seizure onset (4/9)
- Brain imaging: cerebral atrophy
- EEG: slow background activity and diffuse spike waves or polyspike waves
- Video-EEG: in a few cases, possible to record myoclonias, mainly involving upper limbs

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)



Vignoli et al., 2011

Late onset myoclonic epilepsy in Down syndrome – (LOMEDS)



52 yrs., male

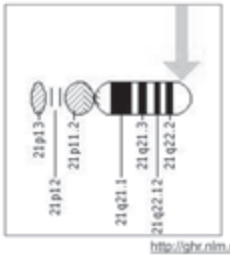
Unverricht-Lundborg syndrome.....

- Onset 6-15 yrs.; stimulus-sensitive myoclonus, and tonic-clonic epileptic seizures
- Late symptoms: ataxia incoordination, intentional tremor, dysarthria
- May have normal lifespan, mentally alert
- Emotional liability, depression, and mild decline in intellectual performance over time
- **Associated to chromosome 21 in a gene in region 21q22.3**

??????

Laura Guilhoto

"Cystatin B gene (stefin B)"



http://ghr.nlm.nih.gov/gene/CSTB

Cytogenetic Location: 21q22.3
Molecular Location on chromosome 21: base pairs 45,193,830 to 45,196,258

Seizures and dementia in Down's syndrome

1. History
2. Down syndrome
3. Down syndrome and aging
4. Down syndrome and Alzheimer disease
5. Down syndrome and late onset myoclonic epilepsy
6. **Conclusions**

Laura Guilhoto

Laura Guilhoto

http://www.fondationlejeune.org/

- http://www.youtube.com/watch?v=jt9o4JPibBI

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Famous people with Down syndrome

Chris Burke | Jane Cameron | Sujeet Desai | Bernadette Resha

??
Phenotipical variation
Mosaicism
Environment

Laura Guilhoto

"Colegas"
"Kikito" Best Film Award of the 40th edition of the Brazilian Gramado Film Festival
Aug/18/2012

Laura Guilhoto

Seizures and dementia in Down's syndrome

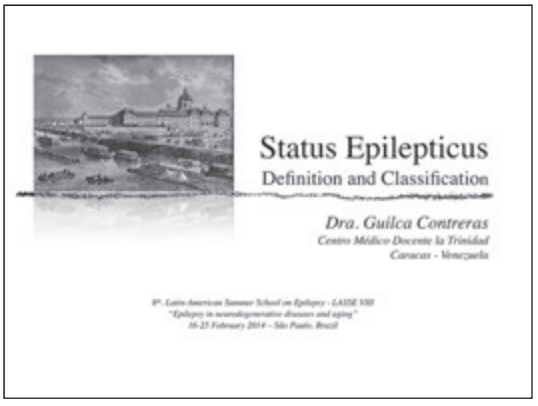
Thank you for your attention!

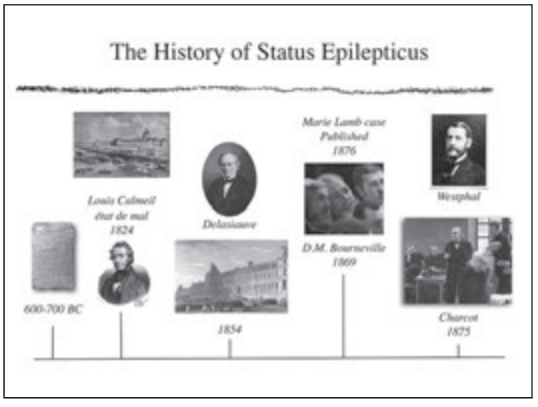
lauraguilhoto@gmail.com
lauraguilhoto@apaesp.org.br

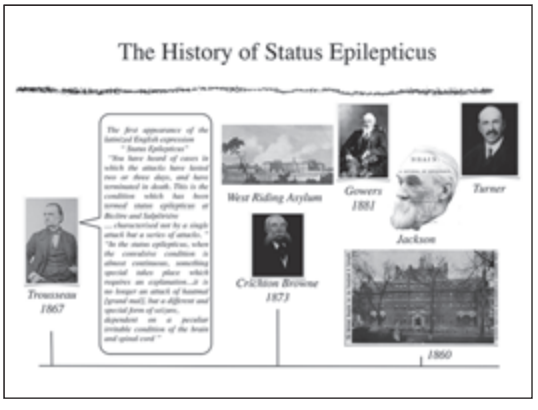
Laura Guilhoto

Guilca Contreras (Venezuela)

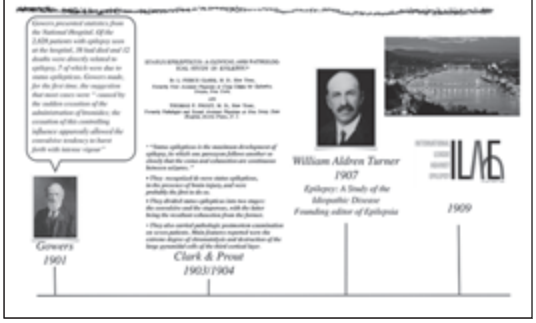
CLASSIFICATION OF STATUS EPILEPTICUS







The History of Status Epilepticus



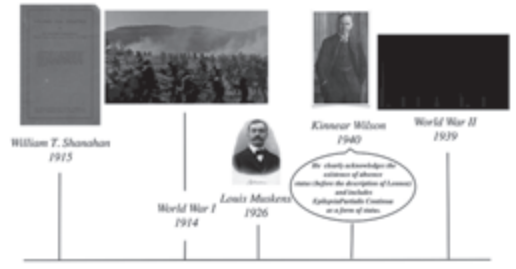
Gowers
1901

Clark & Prout
1903/1904

William Aldren Turner
1907
Epilepsy: A Study of the Idiopathic Disease
Founding editor of *Epilepsia*

1909

The History of Status Epilepticus



William T. Shanahan
1915

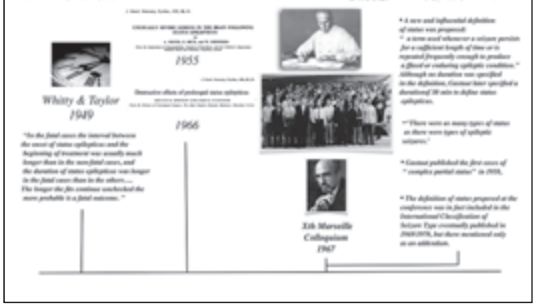
World War I
1914

Louis Muskens
1926

Kinnear Wilson
1940

World War II
1939

The History of Status Epilepticus



Whitty & Taylor
1949

1955

1966

Xth Marseille Colloquium
1967

Classification and Status Epilepticus

George Bernard Shaw

Crude classifications are "the curse of organized life".

- *Classification schemes are necessary in science and medicine.*
- *In science classification schemes can be divided into two distinct orders:*

- *First-order classification schemes: The division of plants and animals into kingdoms, phylum, class, order, family, genus and species is a good example of a first-order classification.*
- *Second-order classification schemes: These schemes are not based on any synoptical, scientific hypothesis (evolution, phylogeny, speciation, underlying physiology, biochemical mechanism, etc), but are in essence, simply definitions–shorthand terms which simply categorise and describe clinical observations.*

Purpose of Classification of Status Epilepticus

1.Clinical communication
2.Treatment
3.Research
- *Epidemiology*
- *Clinical*
- *Genetic*

Definition of terms:
- *Classification*
  - *Clinical (1981 2005/6)*
  - *Epidemiological (1993)*
- *Diagnostic scheme (2001)*
- *Organisation (2010)*

Status Epilepticus Definition & Classification

- ***1970**: Using both clinical and EEG criteria, status epilepticus was subdivided into: generalized convulsive status (tonic-clonic, tonic, clonic and myoclonic), generalized non-convulsive (absence) status, elementary partial status (with several subtypes), complex partial status, and unilateral/erratic status epilepticus (being specific for neonates and small children).*
- ***1981**: Gastaut definition was only slightly modified by the Commission on Classification and Terminology of the International League Against Epilepsy , when the ILAE defined status epilepticus as "a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur". It still confined to the addendum, was simplified further, dropping the "unilateral" category and leaving only a distinction between "partial"and "generalized" status episodes.*
- *Neither definition included a minimal duration of the event, but most experts at the time shared Gastaut's opinion that it should be at least 30 minutes (Gastaut 1967).*

Status Epilepticus Definition & Classification

- *Shorvon 1994: He proposed a more synoptical scheme, which categorised status by age and epilepsy syndrome as well as by seizure type.*

Status Epilepticus Definition & Classification

- *Some facts are taken into account in the ILAE Task Force on Classification and Terminology (Blume et al. **2001**), which defined status as "a seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without interictal resumption of baseline central nervous system function", the latter including not just a disturbance of consciousness, but any kind of neurological deficit persisting in-between seizures. Again however, a precise time limit is not stated.*

- *Since 2000, several authors have started to use operational definitions shortening this time-frame to 5-20 minutes, depending on age and seizure type (Lowenstein et al. 1999).*

Status Epilepticus Definition & Classification

- *Mechanistically, status epilepticus represents the failure of the natural homeostatic seizure-suppressing mechanisms responsible for seizure termination.*
- *The mechanisms involved in initiation and spread of the various types of status epilepticus are, in general, similar to those of self-limited ictal events, but additional factors that need to be considered in determining criteria for classification include:*
  - *Different mechanisms that can prevent seizure termination, for example, mechanisms that prevent active inhibition, desynchronization of hypersynchronous discharges, and depolarization block.*
  - *Progressive features that contribute to subsequent functional and structural brain disturbances.*
  - *Motivational factors.*

ILAE Task Force 2006

- **I. Epilepsia partialis continua (EPC)**
  - A. As occurs with Rasmussen syndrome
  - B. As occurs with focal lesions
  - C. As a component of inborn errors of metabolism
- **II. Supplementary motor area (SMA) status epilepticus**
- **III. Aura continua**
- **IV. Dyscognitive focal (psychomotor, complex partial) status epilepticus**
  - A. Mesial temporal status epilepticus
  - B. Neocortical status epilepticus
- **V. Tonic–clonic status epilepticus**
- **VI. Absence status epilepticus**
  - A. Typical and atypical absence status epilepticus
  - B. Myoclonic absence status epilepticus
- **VII. Myoclonic status epilepticus**
- **VIII. Tonic status epilepticus**
- **IX. Subtle status epilepticus**

Jerome Engel, Jr Epilepsia, Vol. 47, No. 9, 2006

Status Epilepticus Definition & Classification

- *A condition characterised by epileptic seizures that are sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition.* *WHO* ***1973***
- *A seizure that persists for a sufficient length of time or is repeated frecuently enough that recovery between attacks does not occur.* *ILAE Commission* ***1981***
- *A seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without inter-ictal resumption of baseline central nervous system function.*

  ILAE Glossary ***2001***
- *A condition in wich epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms, and with a highly variable pathophysiological, anatomical and aetiological basis.* *Shorvon* ***1994***

Status Epilepticus Definition & Classification

- *Time limit of ten minutes*
- *Semiological components are classified along three axes:*

  1)The type of brain function: ***2)The body part involved:***

- the sensory sphere	*- generalized*
- the autonomic sphere	*- bilateral asymetric*
- the cognitive sphere	*- axial*
- the motor sphere	*- left or right*
	- single body part

  3)The evolution in time:

  - continuous or intermittent seizure activity

  - comprise semiological components

- *abdominal aura ⇒ automotor status*
- *visual aura status ⇒* left eye versive seizure*
- *automotor seizure ⇒* left versive seizure (LOC) ⇒* left clonic seizure ⇒* right clonic seizure*

Status Epilepticus Definition & Classification

- *Traditional classification:*
  - *There were as many types of status as there were types of epileptic seizures (draft 1962, final 1967).*
  - *SE classification mirrored the seizure classification (draft 1964, final 1970).*
- *"a seizure that persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur"... "enduring epileptic condition with reduced/altered consciousness, behavioral and vegetative abnormalities or merely subjective symptoms, without major convulsive movements"ILAE 1981 (1)*
- *Majority of GTCS < 2>3 min (3)*
- *Operational definition: 5 min (4)*
- *..."Mechanistically, SE represents the failure of the natural homeostatic seizure-suppressing mechanisms for seizure termination."...(2)*
- *NCSE Definition 30 min*

1-Commission on Classification (ILAE), Epilepsia 1981; 2-Engel et al. Epilepsia 2006; 3-Theodore et al. Neurology 1994; 4-Lowenstein et al. Epilepsia 1999

Status Epilepticus Definition & Classification

Status epilepticus is a ***prolonged seizure*** *(t1) that might lead to* ***long term consequences*** *(t2) including neuronal death, neuronal injury, and alteration of neuronal networks, depending on type and duration of SE.*

- *Conceptual (= "mechanistic") definition.*
- ***2 Operational dimensions:***
  - *length of seizure (t1).*
  - *time (t2) to long term consequences.*

Treatment, 1867: "In the status epilepticus, when the convulsive condition is almost continuous, something special takes place which requires an explanation"

Status Epilepticus Definition & Classification

Type of SE	Time (t1), when a seizure is likely to be prolonged leading to continuous seizure activity	Time (t2), beyond which long term consequences are increasingly likely (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic-clonic SE	5 minutes	> 30 minutes
SE with dyscognitive symptoms	*5 minutes	*30-60 minutes
Absence status epilepticus	*5 minutes	*unknown
Implications to treatment	Time point 1 determines the earliest time when treatment should be considered or started	Time point 2 determines the time at which status should be controlled to prevent long term consequences

*Best available evidence, but insufficient data to give a definite viewpoint

Status Epilepticus Definition & Classification

Classification of SE: Axis Concept

1. Axis 1 = Status Semiology → Classification of SE Types

2. Axis 2 = Electroencephalography

3. Axis 3 = Etiology

4. Axis 4 = Age

- *List of (specific) age related electroclinical Syndromes with SE (e.g. LGS, JME, CAE, de novo ASE…)*
- *List of (specific) etiologies*
- *List of (special) constellations*

Status Epilepticus Definition & Classification

Classification of SE

Axis 1 Semiology | *Axis 2 EEG* | *Axis 3 Etiology* | *Axis 4 Age*

Clinical Classification of SE

→ *Classification of SE*

Status Epilepticus Definition & Classification

Axis 1 = semiology
→ Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

- *A) With prominent motor symptoms*
  1. *Convulsive SE (syn.: tonic clonic SE, CSE)*
  2. *Myoclonic SE (prominent epileptic myoclonic jerks)*
  3. *Focal motor (including EPC)*
  4. *Tonic SE*
  5. *Hyperkinetic SE*
- *B) Without prominent motor symptoms (NCSE)*
  1. *NCSE with coma*
  2. *NCSE without coma*
     a) Generalized
     b) Focal

Status Epilepticus Definition & Classification

Axis 1 = semiology
→ Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

- *A) With prominent motor symptoms*

1. *Convulsive SE (syn.: tonic clonic SE, CSE)*
   a) Generalized convulsive
   b) Focal onset evolving into bilateral convulsive SE
   c) Unknown whether focal or generalized
2. *Myoclonic SE (prominent epileptic myoclonic jerks)*
   a) With coma
   b) Without coma
3. *Focal motor (including EPC)*
   a) Repeated focal motor seizures (Jacksonian)
   b)Epilepsia Partialis Continua (EPC)
   c) Adversive status
   d) Oculoclonic status
   e) Ictal paresis
4. *Tonic SE*
5. *Hyperkinetic SE*

Status Epilepticus Definition & Classification

Axis 1 = semiology
→ Classification of SE types

Along two taxonomic criteria: motor symptoms and impairment of consciousness

- *B) Without prominent motor symptoms (NCSE)*

1. *NCSE with coma*
2. *NCSE without coma*
   a) Generalized
      a) Typical absence status
      b) Atypical absence status
      c) Myoclonic absence status
   b) Focal
      a) Without impaired consciousness (Aura continua)
         (With autonomic, sensory symptoms, visual, olfactory, gustatory, emotional, auditory symptoms)*
      b) Aphasic SE
      c) With impaired consciousness (dyscognitive SE)
   c) Unknown
      *a) Autonomic SE**

** Differentiation between 2.b.a and 2.c.a has to be discussed*

Status Epilepticus Definition & Classification

Table 1. Definition of nonconvulsive status epilepticus (NCSE)
Nonconvulsive status epilepticus (NCSE) is a term used to denote a range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms.
Notes: 1. NCSE can be most usefully viewed as a form of cerebral response, which is dependent largely on the level of cerebral development of the individual (age and cerebral integrity/development/maturity), epilepsy syndrome, and the anatomical location of the epileptic activity. 2. The electrographic activity can take various forms.

Table 2. Classification of nonconvulsive status epilepticus (NCSE)

Shorvon S. Epilepsia, 48(Suppl. 8):35-38, 2007

Status Epilepticus Definition & Classification

Axis 1 = semiology
→ *Classification of SE types*

Along two taxonomic criteria: motor symptoms and impairment of consciousness

- *Currently indeterminate conditions*
  1. *Epileptic encephalopathies*
  2. *Coma with epileptiform EEG patterns*
  3. *Behavioural disturbance (e.g psychosis) in patients with epilepsy*
  4. *Acute confusional states (e.g delirium) with epileptiform EEG patterns*

Status Epilepticus Definition & Classification

Classification of SE

Axis 1 Semiology | *Axis 2 EEG* | *Axis 3 Etiology* | *Axis 4 Age*

Ictal EEG correlates

→ *Classification of SE*

Status Epilepticus Definition & Classification

American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version

Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, Mani R, Arif H, Jette N, Minazad Y, Kerrigan JF, Vespa P, Hantus S, Chapman J, Young GB, So E, Kaplan PW, Nuwer MR, Fountain NB and Drislane FW.

Objective: To standardize terminology of periodic and rhythmic EEG patterns in the critically ill in order to aid future research involving such patterns. Our goal is to avoid terms with clinical connotations and to define terms thoroughly enough to ensure adequate inter-rater reliability.

Not included in this nomenclature: Unequivocal electrographic seizures including the following: Generalized spike-wave discharges at 3½ or faster, and clearly evolving discharges of any type that reach a frequency >4/s, whether focal or generalized. These would still be referred to as electrographic seizures. However, their prevalence, duration, frequency and relation to stimulation should be stated as described below when being used for research purposes.

Status Epilepticus Definition & Classification

Classification of SE

Axis 1 Semiology | *Axis 2 EEG* | *Axis 3 Etiology* | *Axis 4 Age*

Categories of etiology

→ *Classification of SE*

Status Epilepticus Definition & Classification

Classification of SE: Axis 3 Etiology

1. *Known (syn. symptomatic)*
    - *a) Acute (e.g.: stroke, intoxication, malaria, encephalitis, etc.)*
    - *b) Remote (e.g. posttraumatic, postencephalitic, poststroke, etc.)*
    - *c) Progressive (e.g. glioblastoma, Lafora's disease and other PMEs)*
    - *d) SE in defined electroclinical syndromes*
2. *Unknown (syn. cryptogenic)*

Status Epilepticus Definition & Classification

Uncommon Causes of SE

1. *Immunologically mediated disorders*
2. *Mitochondrial diseases*
3. *Uncommon infective disorders*
4. *Genetic disorders*
5. *Drugs or toxins*

SEIZURES IN SPECIAL AND SEVERE SITUATIONS

Causes of status epilepticus

Rogvi Trinka, Julia Höfler, and Alexander Zerbs

Immunologic disorders causing status epilepticus

Paraneoplastic encephalitis
Hashimoto encephalopathy
Anti-NMDA-receptor encephalitis
Anti-VGKC-receptor encephalitis
Rasmussen encephalitis
Cerebral lupus
Adult-onset Still disease
Anti-GAD antibody-associated encephalitis
Goodpasture syndrome
Thrombotic thrombocytopenic purpura
Antibody-negative limbic encephalitis

NMDA, N-methyl-D-aspartate; GAD, glutamate acid decarboxylase.

Mitochondrial diseases causing status epilepticus

Alpers disease
Occipital lobe epilepsy/mitochondrial spinocerebellar ataxia and epilepsy (POLG6)
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
Leigh syndrome
Myoclonic encephalopathy with ragged-red fibers (MERRF)
Neuropathy, ataxia, and retinitis pigmentosa (NARP)

Trinka E., et al. Epilepsia, 51(Suppl. 4):177–178, 2012

Uncommon infectious disease causing status epilepticus

Atypical bacterial infections	Viral infections	Prion disease	Other infections
Bartonella/cat-scratch disease	HIV and HIV-related infections	Creutzfeldt-Jakob disease	Paracoccidioidomycosis
Coxiella/burnout (Q fever)	West Nile encephalitis		Pyogenic brain abscess
Neurosyphilis	JC virus (progressive multifocal leukoencephalopathy)		Phaeomycosis
Scrub typhus	Parvovirus B19		
Shigellosis	Varicella encephalitis		
Mycoplasma pneumonia	Subacute sclerosing panencephalitis		
Chlamydophila/psittaci	Measles encephalitis		
	Rubella encephalitis		
	Ross sarcoma virus		
	(RSV)-associated SE		
	Poliomyelohalomyelitis		
	St. Louis encephalitis		

Trinka E., et al. Epilepsia, 51(Suppl. 4):177–178, 2012

Status epilepticus due to genetic diseases				
Chromosomal aberrations	Inborn errors of metabolism	Malformations of cortical development	Neurocutaneous syndromes	Others
Ring chromosome 20	Porphyria	Focal cortical dysplasia	Sturge-Weber syndrome	Rett's syndrome
Angelman syndrome	Menkes' disease	Hemimegalencephaly	Tuberous sclerosis	Dravet syndrome and SCN1A gene mutation spectrum
Wolf-Hirschhorn syndrome	Wilson's disease	Polymicrogyria		Migrating partial seizures in infancy
Fragile X syndrome	Alexander's disease	Heterotopias		Pyridoxine dependency
[illegible] syndrome	[illegible] deficiency	Schizencephaly		Familial hemiplegic migraine
Ring chromosome 17	Ornithine transcarbamylase (OTC) deficiency			Lafora's disease
	Hyperprolinemia			Dentato-rubro-pallido-luysian atrophy
	Maple syrup urine disease			Infantile onset spinocerebellar ataxia
	3-Methylcrotonyl CoA carboxylase deficiency			[illegible] syndrome
	Lysinuric protein intolerance			[illegible]
	Hydroxyglutaric aciduria			[illegible] mutation
	[illegible]			[illegible] syndrome
	Kufs disease			[illegible]
	Late infantile neuronal lipofuscinosis			Cockayne syndrome
	Beta-ureidopropionase deficiency			Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
	3-Hydroxyacyl CoA dehydrogenase deficiency			[illegible] syndrome
				[illegible] syndrome
	Carnitine palmitoyltransferase			[illegible] mutation
				[illegible] mutation
	Succinic semialdehyde dehydrogenase deficiency			Malignant hyperthermia

Trinka E., et al. Epilepsia, 53(Suppl. 4):127–138, 2012

Status Epilepticus Definition & Classification

Classification of SE

Axis 1 Semiology	Axis 2 EEG	Axis 3 Etiology	Axis 4 Age

Age groups

→ *Classification of SE*

Status Epilepticus Definition & Classification

Classification of SE: Axis 4 Age

1. *Neonatal period*
2. *Infancy and Childhood*
3. *Adolescence and adulthood*
4. *Elderly*

MOLECULAR NATURE OF STATUS EPILEPTICUS

Influence of brain development on status epilepticus

Gregory L. Holmes

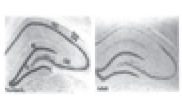


Figure 1.

Status Epilepticus Definition & Classification

Age Related Disorders and Electroclinical Syndromes with SE

1. *SE occurring in the neonatal and infantile epilepsy syndromes*
   a) *Tonic Status in Ohtahara Syndrome*
   b) *Myoclonic status in Dravet's syndrome*
   c) *Febrile SE*
      i. *With bilateral motor symptoms*
      ii. *With unilateral motor symptoms*
      iii. *Without motor symptoms (?)*
2. *SE occurring predominately in childhood and adolescence*
   a) *NCSE in Early onset Childhood Occipital Early Epilepsy (Panayiotopoulos syndrome)*
   b) *NCSE in childhood epileptic encephalopathies (e.g., myoclonic-astatic epilepsy, Ring chromosome 20, Angelman syndrome)*
   c) *Tonic status in Lennox Gastaut Syndrome*
   d) *Myoclonic Status in Down Syndrome*
   e) *Absence Status in Juvenile Absence Epilepsy*
   f) *Myoclonic Status in Juvenile Myoclonic Epilepsy*
   g) *Myoclonic Status in Progressive Myoclonus Epilepsies*
   h) *FIRES*
3. *SE occurring only in adults and elderly*
   a) *De Novo (or relapsing) absence status of later life*

Status Epilepticus Epidemiology

–*SE minimal incidence: 10–20/100,000 in Switzerland, Germany, Italy and in the white population of the USA.*

–*The incidence of SE in the African-American population of Richmond Virginia, is three times as high as compared to the Caucasian population.*

–*In North London, Asian children (mostly from the Indian subcontinent) had a relative risk to develop status of 6.5.*

–*In developing countries where 80% of epileptic patients live, SE data and characteristics have not been well studied. In 1997, Medina et al., reported that in Salamá, a rural area of Honduras, 47% of epileptic patients had had at least one episode of SE, was more prevalent in children, convulsive type was the most common and the main causes were medication supression and neurocysticercosis.*

– *SE is age related with the highest incidences in young children and the elderly of an age of 60 and above. The incidence in the elderly is about 3–10 times that of younger adults.*

–*Nonconvulsive types of SE make up about 25–50% of all SE including some 1–6% of cases with absence SE and 44% with complex partial SE.*

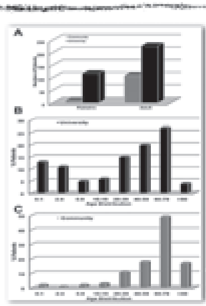
Jallon et al., Lancet 1999; Coeytaux et al., Neurology 2000; Knake et al., Epilepsia 2001; Vignatelli et al., Epilepsia 2003; Vignatelli et al., Eur J Neurol 2005; DeLorenzo et al., Clin Neurophysiol. 1995; DeLorenzo et al., Neurology 1996; Hesdorffer et al., Neurology 1998; DeLorenzo, Adv Neurol 2006; Chin et al., Lancet 2006; Wu et al., Neurology 2002; Medina M., et al. VIII Panamerican Epilepsy Congress 1997.

Status Epilepticus Epidemiology

- *Case fatality of SE in general lies between 1.9% and 40% and depends mainly on age (over 65 years > 20–64 years > under 20 years of age), sex (m > w), and etiology.*
- *Hypoxia, stroke, CNS infections and metabolic disorders, are associated with the highest case fatalities of up to 80%, whereas, low antiepileptic drug levels, fever, alcoholrelated, and traumatic-related etiologies were associated with low mortalities*
- *Long-term case fatality likewise depends on etiology and age as well as status type and duration.*
- *Anoxia and hypoxia are associated with the highest long-term mortality in children and adults, followed by acute symptomatic and remote symptomatic brain damage.*
- *Forty percent of subjects who survived the first 30 days after an incident episode of SE die within the next 10 years.*

Jallon et al., Lancet 1999; Coeytaux et al., Neurology 2000; Knake et al., Epilepsia 2001; Vignatelli et al., Epilepsia 2003; Vignatelli et al., Eur J Neurol 2005; DeLorenzo et al., Clin Neurophysiol. 1995; DeLorenzo et al., Neurology 1996; Hesdorffer et al., Neurology 1998; DeLorenzo, Adv Neurol 2006; Chin et al., Lancet 2006; Wu et al., Neurology 2002.

Status Epilepticus Epidemiology



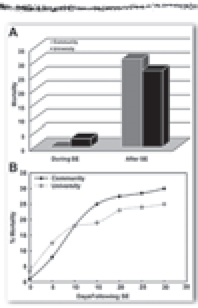
Seizure. 2009 July; 18(6): 405–411. doi:10.1016/j.seizure.2009.02.003.

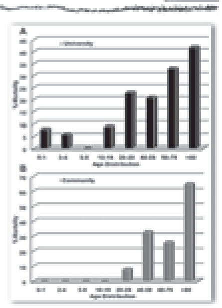
Comparisons of the mortality and clinical presentations of status epilepticus in private practice community and university hospital settings in Richmond, Virginia

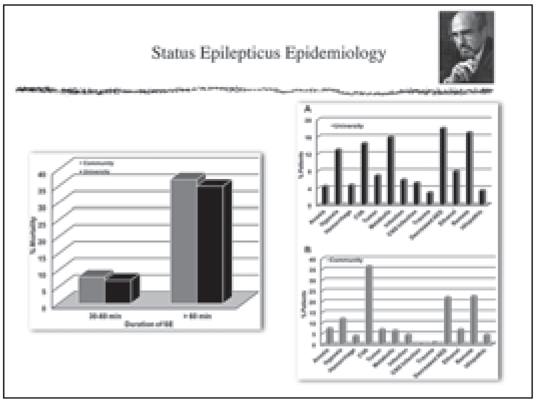
Robert J. DeLorenzo, Babak Kirmani, Laxmikant S. Deshpande, Vamsi Jakkampudi, Alan R. Towne, Elizabeth Waterhouse, Linda Garnett, and Ramesh Ramakrishnan

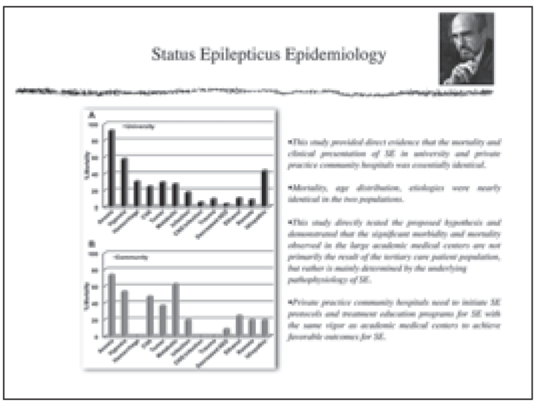
- *119 patients treated for status epilepticus (SE) in private practice community hospitals and 344 SE patients treated in the VCU university hospitals in Richmond, Virginia USA over a two-year period to test the hypothesis that SE presents with the same mortality and clinical patterns in both clinical settings.*
- *SE was defined as on continuous or intermittent seizure activity without regaining consciousness lasting for 30 minutes or longer.*
- *Seizure duration was defined as the time from the onset of SE until both clinical and electrographic evidence demonstrated that seizure activity had subsided.*
- *The pediatric population included patients between the ages of 1 month and 15 years of age. The adult group included patients aged 16 years and older.*

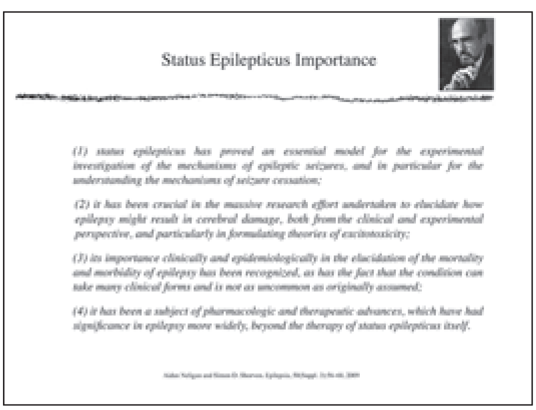
Status Epilepticus Epidemiology

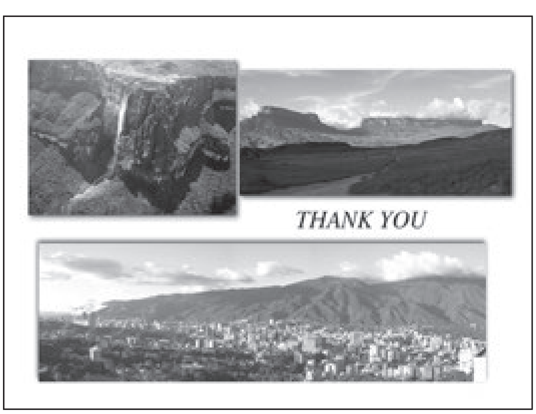





Status Epilepticus Epidemiology
Community
University
% Mortality
30-60 min
> 60 min
Duration of SE
A
B

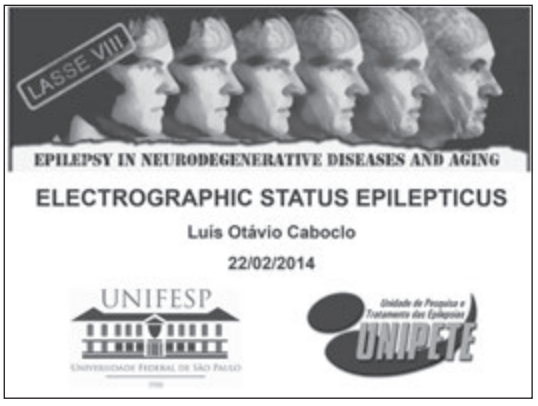

Status Epilepticus Epidemiology
A
University
B
Community
•This study provided direct evidence that the mortality and clinical presentation of SE in university and private practice community hospitals was essentially identical.
•Mortality, age distribution, etiologies were nearly identical in the two populations.
•This study directly tested the proposed hypothesis and demonstrated that the significant morbidity and mortality observed in the large academic medical centers are not primarily the result of the tertiary care patient population, but rather is mainly determined by the underlying pathophysiology of SE.
•Private practice community hospitals need to initiate SE protocols and treatment education programs for SE with the same vigor as academic medical centers to achieve favorable outcomes for SE.


Status Epilepticus Importance
(1) status epilepticus has proved an essential model for the experimental investigation of the mechanisms of epileptic seizures, and in particular for the understanding the mechanisms of seizure cessation;
(2) it has been crucial in the massive research effort undertaken to elucidate how epilepsy might result in cerebral damage, both from the clinical and experimental perspective, and particularly in formulating theories of excitotoxicity;
(3) its importance clinically and epidemiologically in the elucidation of the mortality and morbidity of epilepsy has been recognized, as has the fact that the condition can take many clinical forms and is not as uncommon as originally assumed;
(4) it has been a subject of pharmacologic and therapeutic advances, which have had significance in epilepsy more widely, beyond the therapy of status epilepticus itself.


THANK YOU

Luis Otávio Caboclo (Brazil)

ELECTROENCEPHALOGRAPHIC STATUS EPILEPTICUS



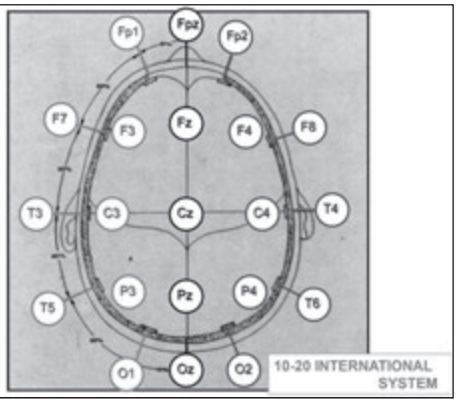
ELECTROGRAPHIC STATUS EPILEPTICUS

- ✓ Electroencephalogram
- ✓ Introduction
- ✓ Definitions and Classification
- ✓ Diagnosis
- ✓ Treatment
  - what we know...
  - what we don't know...
  - what we need to know better!

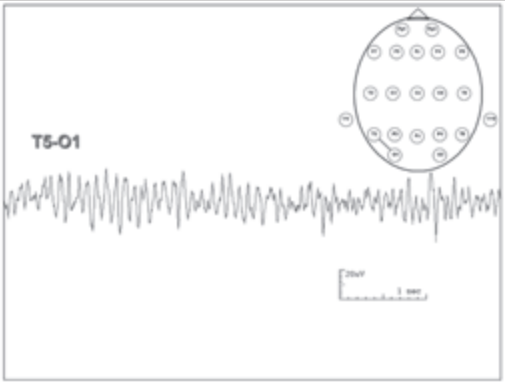
ELECTROGRAPHIC STATUS EPILEPTICUS

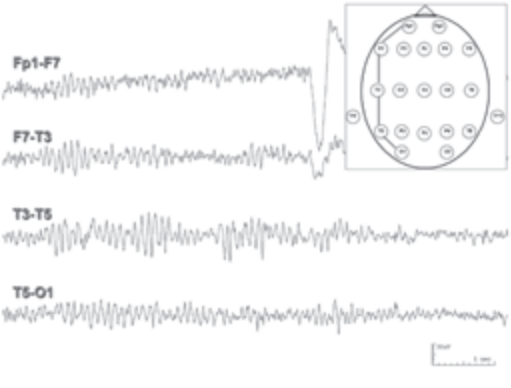
ELECTROGRAPHIC STATUS EPILEPTICUS

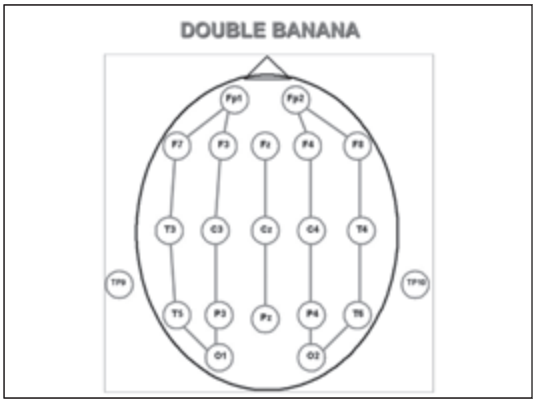
ELECTROENCEPHALOGRAM

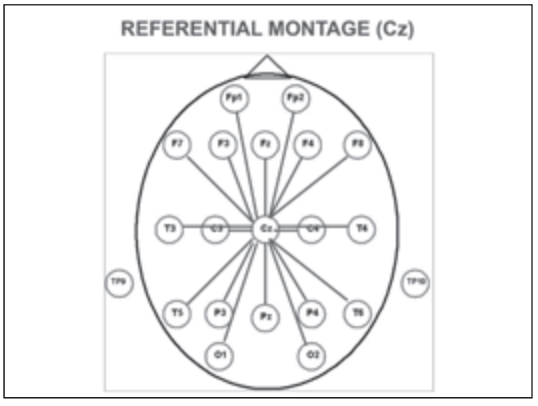


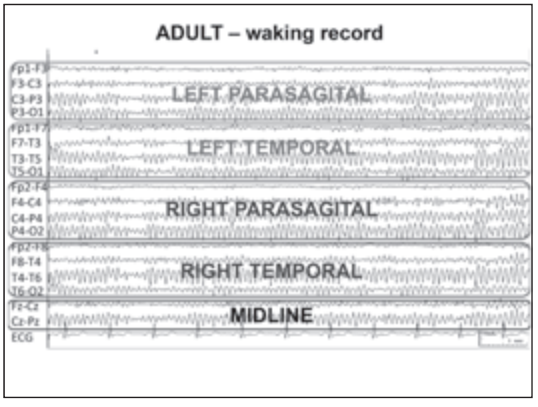
10-20 INTERNATIONAL SYSTEM

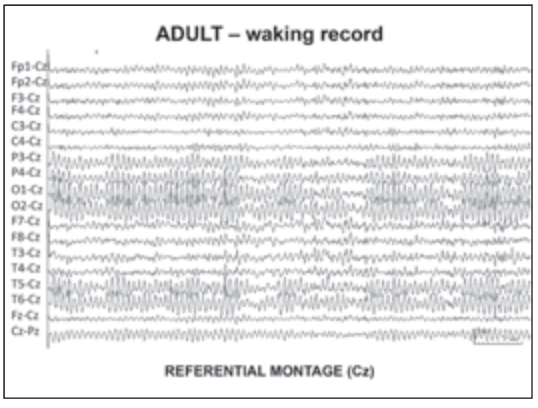


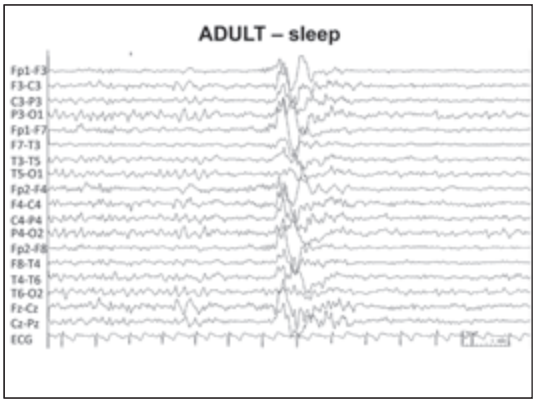


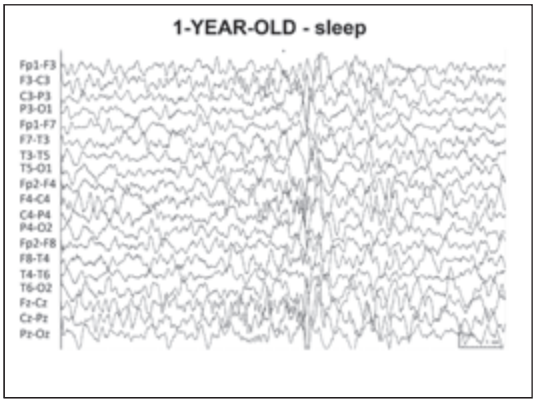

DOUBLE BANANA
Fp1
Fp2
F7
F3
Fz
F4
F8
T3
C3
Cz
C4
T4
TP9
TP10
T5
P3
Pz
P4
T6
O1
O2

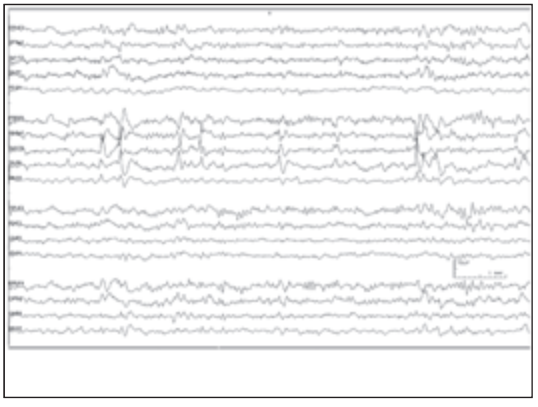

REFERENTIAL MONTAGE (Cz)
Fp1
Fp2
F7
F3
Fz
F4
F8
T3
C3
Cz
C4
T4
TP9
TP10
T5
P3
Pz
P4
T6
O1
O2

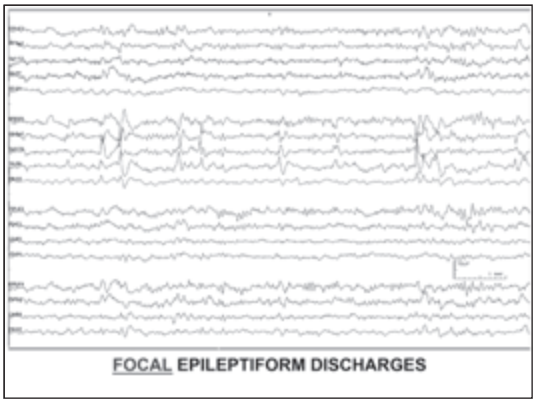

ADULT – waking record
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
ECG
LEFT PARASAGITAL
LEFT TEMPORAL
RIGHT PARASAGITAL
RIGHT TEMPORAL
MIDLINE

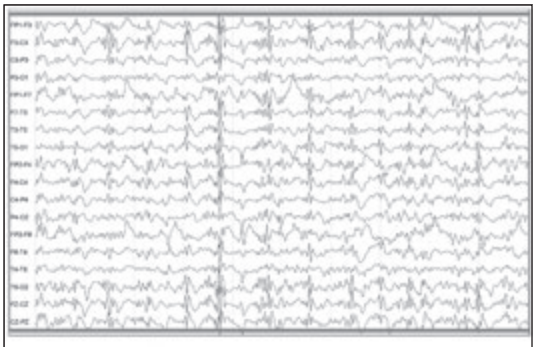

ADULT – waking record
Fp1-Cz
Fp2-Cz
F3-Cz
F4-Cz
C3-Cz
C4-Cz
P3-Cz
P4-Cz
O1-Cz
O2-Cz
F7-Cz
F8-Cz
T3-Cz
T4-Cz
T5-Cz
T6-Cz
Fz-Cz
Cz-Pz
REFERENTIAL MONTAGE (Cz)


ADULT – sleep
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
ECG

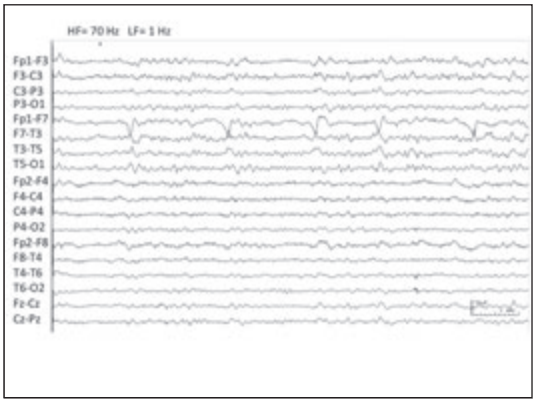

1-YEAR-OLD - sleep
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
Pz-Oz

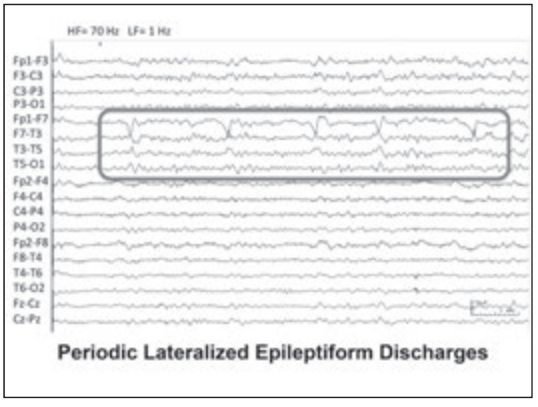



FOCAL EPILEPTIFORM DISCHARGES

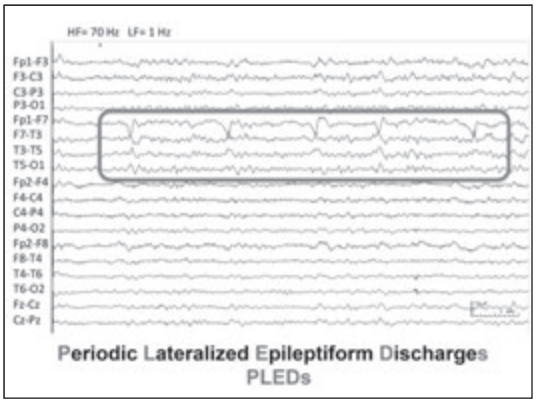


GENERALIZED EPILEPTIFORM DISCHARGES

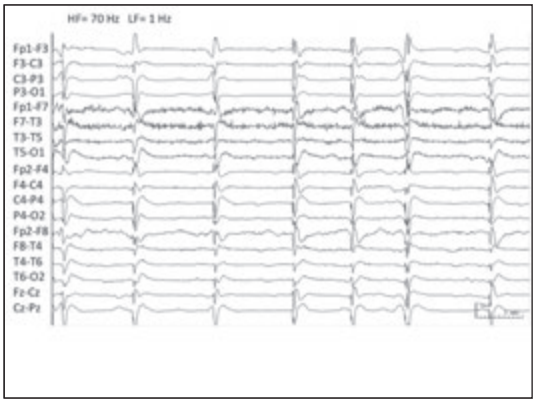


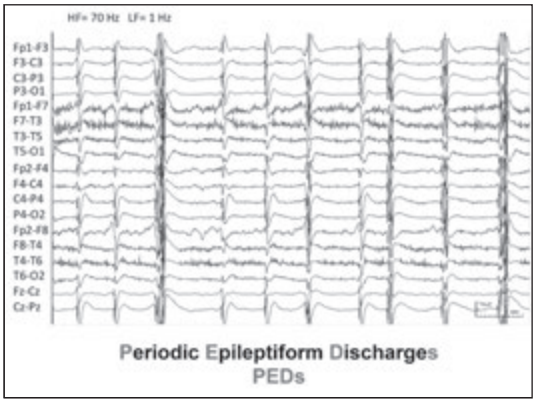


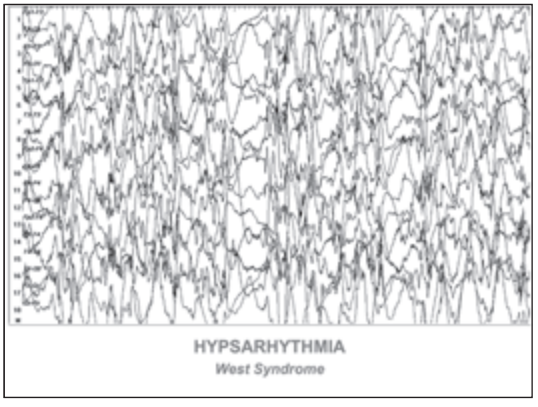
Periodic Lateralized Epileptiform Discharges

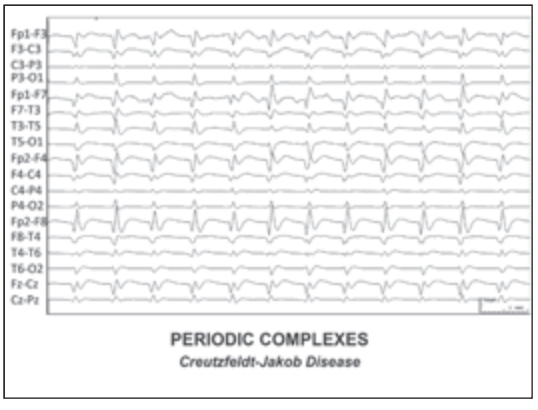


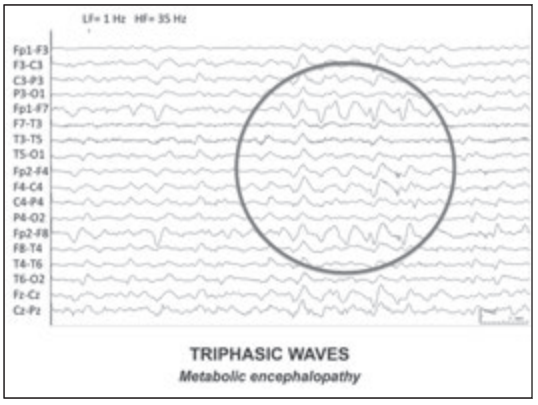
Periodic Lateralized Epileptiform Discharges
PLEDs


HF= 70 Hz LF= 1 Hz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz


HF= 70 Hz LF= 1 Hz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
Periodic Epileptiform Discharges
PEDs

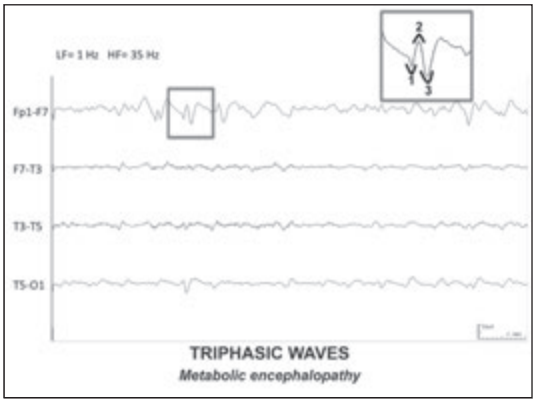

HYPSARHYTHMIA
West Syndrome


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
PERIODIC COMPLEXES
Creutzfeldt-Jakob Disease



TRIPHASIC WAVES

Metabolic encephalopathy



TRIPHASIC WAVES

Metabolic encephalopathy

ELECTROGRAPHIC STATUS EPILEPTICUS

ELECTROGRAPHIC STATUS EPILEPTICUS

"A range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms."

ELECTROGRAPHIC STATUS EPILEPTICUS

NONCONVULSIVE STATUS EPILEPTICUS

"A range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms."

ELECTROGRAPHIC STATUS EPILEPTICUS

NONCONVULSIVE STATUS EPILEPTICUS

"A range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms."

- ✓ *Electrographic seizure activity: may exist without obvious clinical "seizures"*
- ✓ *Electrographic seizure activity can take various forms*

ELECTROGRAPHIC STATUS EPILEPTICUS

NONCONVULSIVE STATUS EPILEPTICUS

"A range of conditions in which electrographic seizure activity is prolonged and results in nonconvulsive clinical symptoms."

"A form of epileptic cerebral response that is largely dependent on…
the level of cerebral development and integrity,
the presence or absence of encephalopathy,
the type of epilepsy syndrome and
the anatomical locations of the epileptic activity"

Shorvon, 2009

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY
NCSE IN CHILDHOOD
NCSE IN CHILDHOOD AND ADULT LIFE
NCSE CONFINED TO LATE ADULT LIFE

** BOUNDARY SYNDROMES*

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY
NCSE IN CHILDHOOD
NCSE IN CHILDHOOD AND ADULT LIFE
NCSE CONFINED TO LATE ADULT LIFE

** BOUNDARY SYNDROMES*

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY

- ✓ **Ohtahara syndrome**
- ✓ **West syndrome**
- ✓ **Dravet syndrome**
- ✓ **NCSE related to infection, anoxia, metabolic and developmental cases**

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY
NCSE IN CHILDHOOD
NCSE IN CHILDHOOD AND ADULT LIFE
NCSE CONFINED TO LATE ADULT LIFE

** BOUNDARY SYNDROMES*

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN CHILDHOOD

- ✓ **Benign rolandic epilepsy**
- ✓ **Panayiotopoulos syndrome: autonomic SE**
- ✓ **Ring chromosome 20 syndrome**
- ✓ **Angelman syndrome**
- ✓ **Rett syndrome**
- ✓ **Electrical SE in slow-wave sleep**
- ✓ **Landau-Kleffner syndrome**

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY
NCSE IN CHILDHOOD
NCSE IN CHILDHOOD AND ADULT LIFE
NCSE CONFINED TO LATE ADULT LIFE

** BOUNDARY SYNDROMES*

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN CHILDHOOD AND ADULT LIFE

With epileptic encephalopathy

- ✓ **Lennox-Gastaut syndrome**

Without epileptic encephalopathy

- ✓ **Typical absence SE**
- ✓ **Complex partial SE**
- ✓ **NCSE in the postictal phase of tonic-clonic seizures**
- ✓ **Subtle SE**
- ✓ **Aura continua**

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY
NCSE IN CHILDHOOD
NCSE IN CHILDHOOD AND ADULT LIFE
NCSE CONFINED TO LATE ADULT LIFE

** BOUNDARY SYNDROMES*

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE CONFINED TO LATE ADULT LIFE

De novo absence SE of late onset

**** usually precipitated by psychotropic drug withdrawal (usually benzodiazepines) or abuse***

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

NCSE IN THE NEONATAL PERIOD AND INFANCY
NCSE IN CHILDHOOD
NCSE IN CHILDHOOD AND ADULT LIFE
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** BOUNDARY SYNDROMES*

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

** BOUNDARY SYNDROMES*

- ✓ **Conditions in which it is not clear to what extent the symptoms are due to NCSE**
- ✓ **Patients exhibit clinical symptoms associated with ongoing activity on the EEG, that could be interpreted as NCSE**

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

** BOUNDARY SYNDROMES*

- ✓ **Conditions in which it is not clear to what extent the symptoms are due to NCSE**
- ✓ **Patients exhibit clinical symptoms associated with ongoing activity on the EEG, that could be interpreted as NCSE**

However… To what extent are the symptoms the consequence of this electrographic disturbance (and therefore due to NCSE)?

NON CONVULSIVE STATUS EPILEPTICUS

CLASSIFICATION

** BOUNDARY SYNDROMES*

- **Myoclonic SE in coma in the context of acute severe brain injury**
- **Epileptic encephalopathies of childhood**
- **Epileptic pychosis and behavior disturbance**
- **Confusion states with epileptiform EEG changes (drug-induced or metabolic)**

NON CONVULSIVE STATUS EPILEPTICUS

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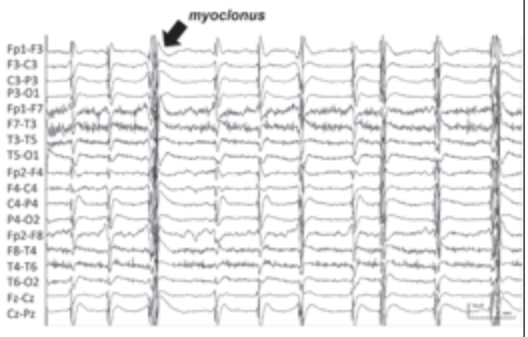

POST-ANOXIC MYOCLONIC STATUS EPILEPTICUS

NON CONVULSIVE STATUS EPILEPTICUS

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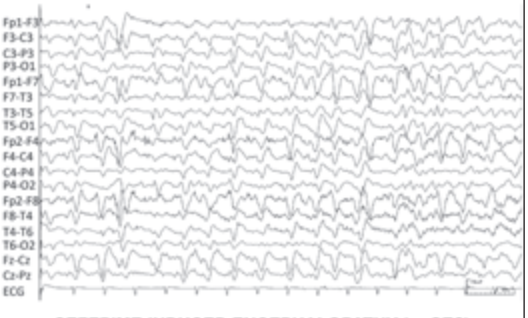


CEFEPIME-INDUCED ENCEPHALOPATHY (or SE?)

STATUS EPILEPTICUS: Definitions

STATUS EPILEPTICUS (SE):

Status epilepticus is a prolonged seizure (t1) that might lead to long term consequences (t2) including neuronal death, neuronal injury, and alteration of neuronal networks, depending on type and duration of SE.

STATUS EPILEPTICUS: Classification

TYPE OF STATUS EPILEPTICUS	Time t1, when a seizure is likely to be prolonged, leading to continuous seizure activity	Time t2, beyond which long term consequences are increasingly likely
Tonic-clonic	5 minutes	30 minutes
SE with dyscognitive symptoms (complex-partial)	5 minutes *	30-60 minutes *
Absence	2 minutes *	unknown

* best available evidence

STATUS EPILEPTICUS

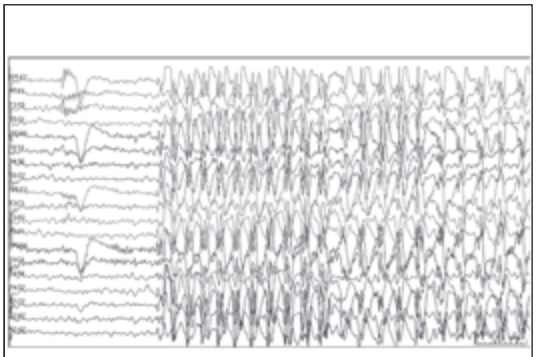
Absence Status Epilepticus

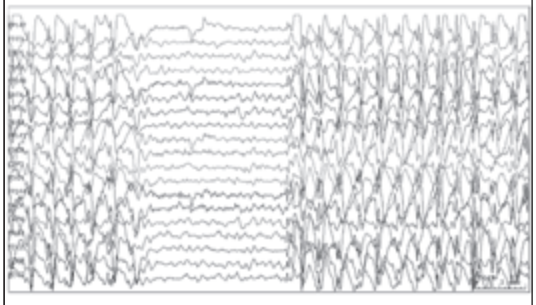
- ✓ Childhood Absence Epilepsy
- ✓ Juvenile Absence Epilepsy
- ✓ Juvenile Myoclonic Epilepsy
- ✓ Eyelid Myoclonia with Absences
- ✓ Perioral Myoclonia with Absences
- ✓ Idiopathic Generalized Epilepsy with GTCS only
- ❖ De novo absence status

"ambulatory status epilepticus"

- ✓ 16-year-old boy
- ✓ frequent episodes of "strange fits" since childhood, reported by his mother
- ✓ one week before admission: GTCS
- ✓ initiated treatment with carbamazepine
- ✓ on admission: confused, slowed mentation

VIDEO: ABSENCE STATUS





STATUS EPILEPTICUS

Absence Status Epilepticus

- ✓ "ambulatory status epilepticus"
- ✓ very low morbidity and mortality
- ✓ no evidence for neurological damage and/or long term consequences
- ✓ treatment: avoid sedative drugs

STATUS EPILEPTICUS

Complex Partial Status Epilepticus

- ✓ various syndromes of lobar epilepsies (mainly frontal and temporal lobe)
- ✓ nonconvulsive status epilepticus in critically ill patients

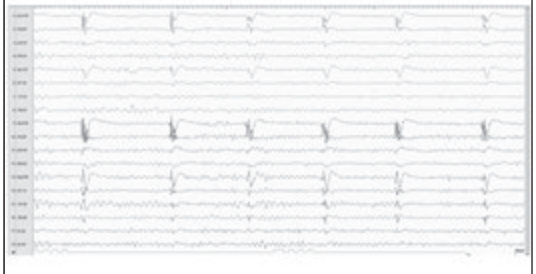
STATUS EPILEPTICUS

Complex Partial Status Epilepticus

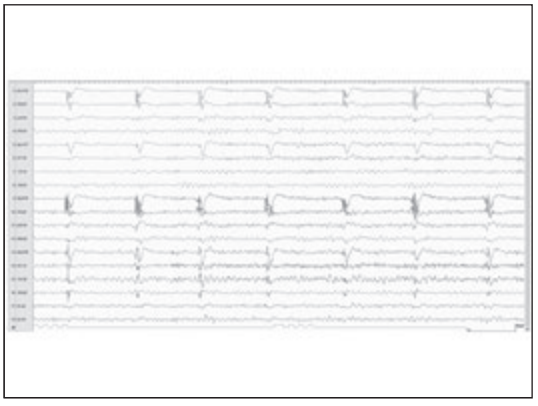
- ✓ various syndromes of lobar epilepsies (mainly frontal and temporal lobe)
- ✓ nonconvulsive status epilepticus in critically ill patients

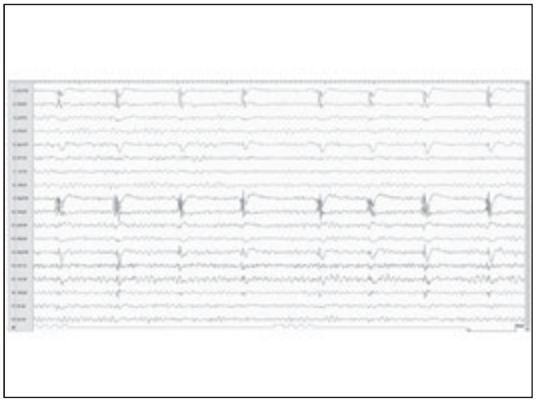
"status epilepticus in patients in coma"

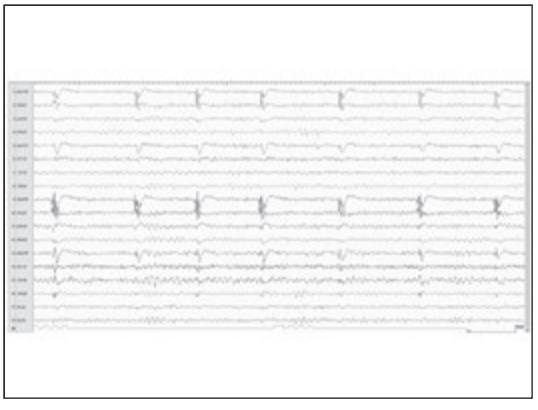
- ✓ 63-year-old woman, previously healthy
- ✓ one week before admission: GTCS
- ✓ good recovery; discharged without treatment
- ✓ one day before admission: facial "spasms" on the right
- ✓ on admission: slightly confused, facial clonic movements on the right

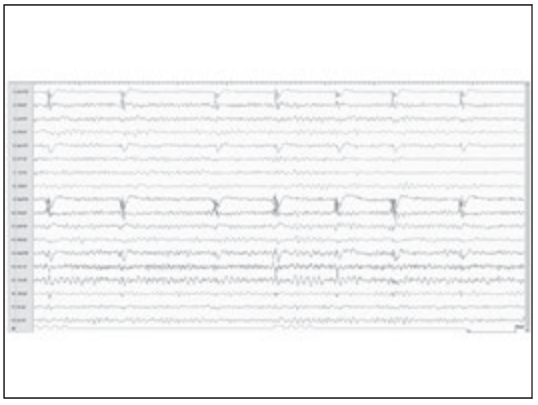


Video MPS 1

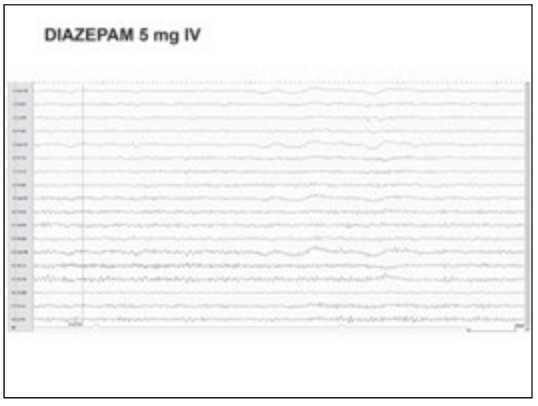


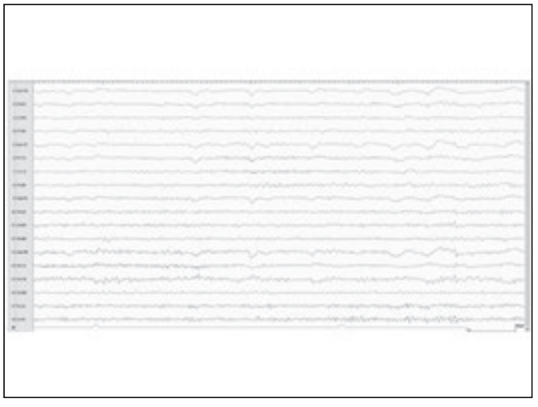






DIAZEPAM 5 mg IV

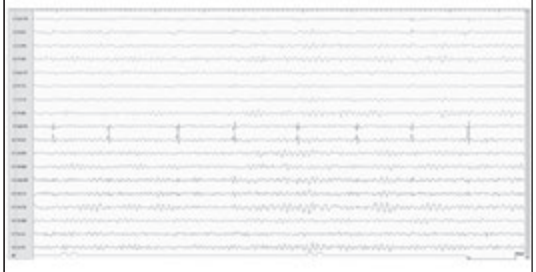


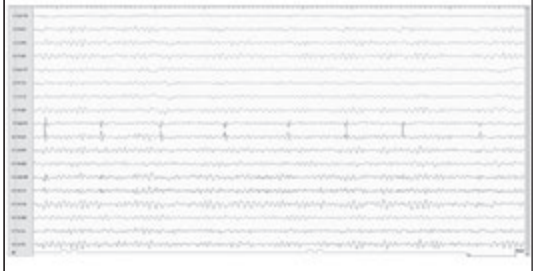


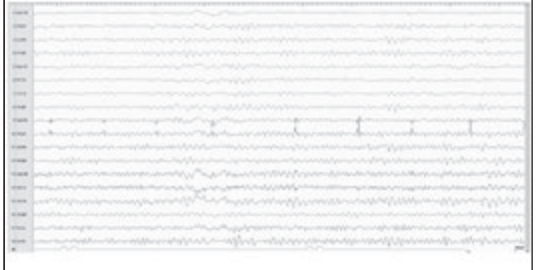
5 minutes later…

Video MPS 2

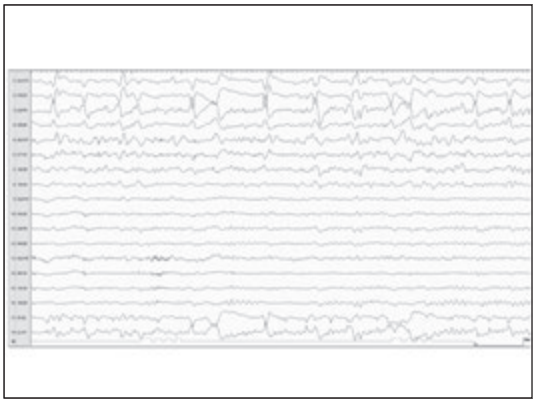
5 minutes later…





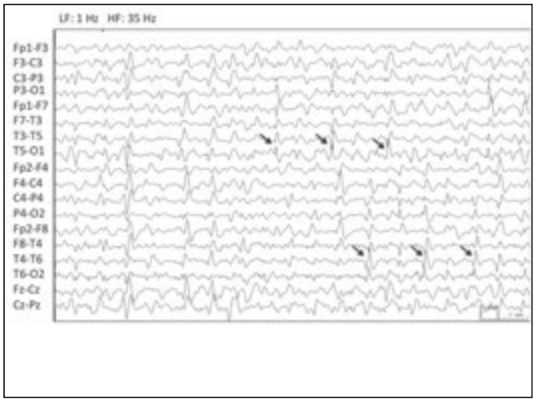


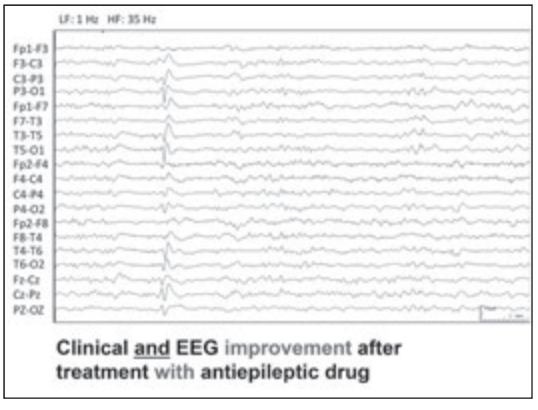
- ✓ 69-year-old woman
- ✓ left frontal meningioma operated four years before
- ✓ woke-up “strange”, with alteration of speech
- ✓ on admission: confused, fluent aphasia
- ✓ MRI: no acute lesions



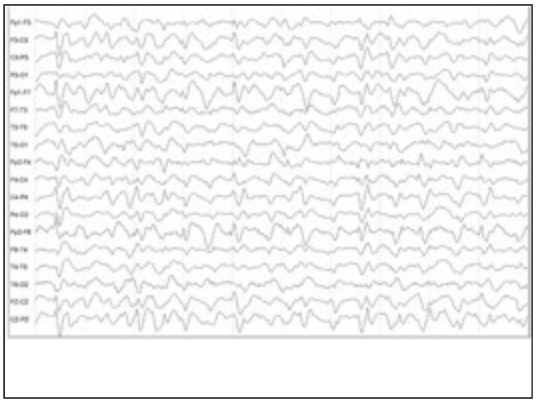
However…

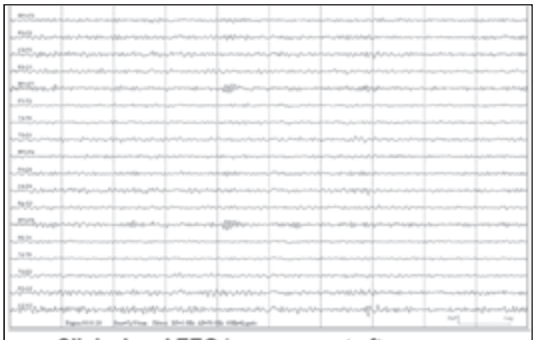
… EEG isn't always *that* easy!





Clinical and EEG improvement after treatment with antiepileptic drug





Clinical and EEG improvement after treatment without antiepileptic drug

EEG criteria for nonconvulsive status epilepticus

Epilepsia

Peter W. Kaplan

- Repetitive generalized or focal spikes, polyspike, sharp waves, spike-and-wave or sharp-and-slow wave complexes at >2.5/second.
- Above, with discharges <2.5/second but with EEG and clinical improvement after rapid onset antiepileptic drugs, typically BZPs. Testing for patient responsiveness and improvement in EEG; increases in EEG reactivity and appearance of EEG background activity.
- Above, with discharges < 2.5/sec with focal ictal phenomena (e.g., facial twitching, gaze deviation, nystagmus, limb myoclonus).
- Rhythmic waves (theta-delta) at >0.5 Hz with a) incrementing onset (increase in voltage with increase or decrease in frequency), b)evolution in pattern (increase or decrease in frequency (>1 Hz), or location [changes in discharge voltage (amplitude) or morphology are not sufficient], or c) decrementing termination (voltage or frequency), d) post-PEDs background slowing or attenuation. A,b,c may be acutely abolished by IV BZPs.

Kaplan. Epilepsia 2007; 48 (Suppl. 8): 39-41

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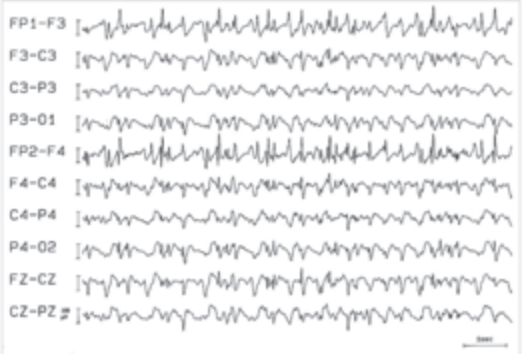
Kaplan. Epilepsia 2007; 48 (Suppl. 8): 39-41

- 54-year-old woman
- epilepsy since childhood
  - ✓ absence seizures
  - ✓ generalized tonic-clonic seizures
- history of poor adherence to medical treatment
- one day history of confusion and altered behavior, with occasional myoclonus

Idiopathic generalized epilepsy: Absence Status



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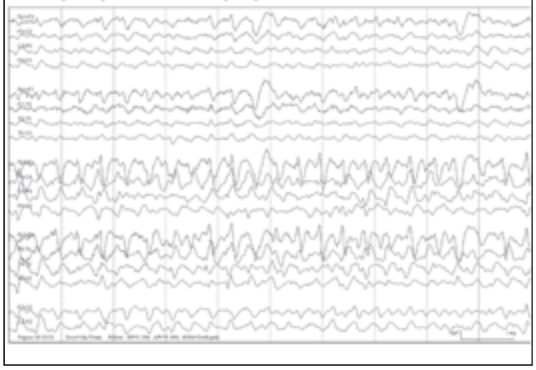
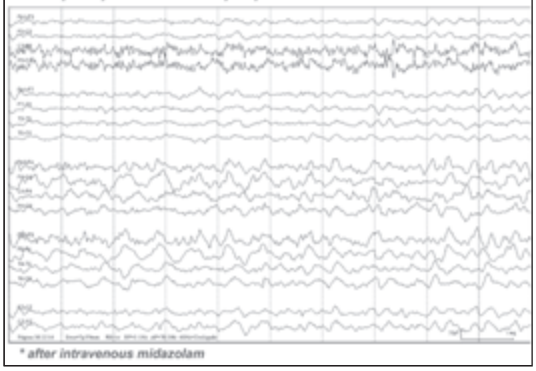
Kaplan. Epilepsia 2007; 48 (Suppl. 8): 39-41

- 65-year-old man
- right temporal meningioma operated two years before
- fever and cough for three days
- one-day history of somnolence and confusion

Complex partial status epilepticus



Complex partial status epilepticus



** after intravenous midazolam*

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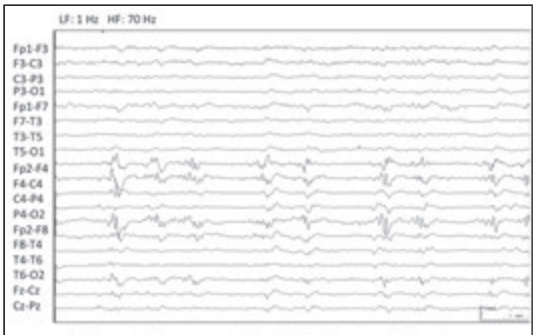
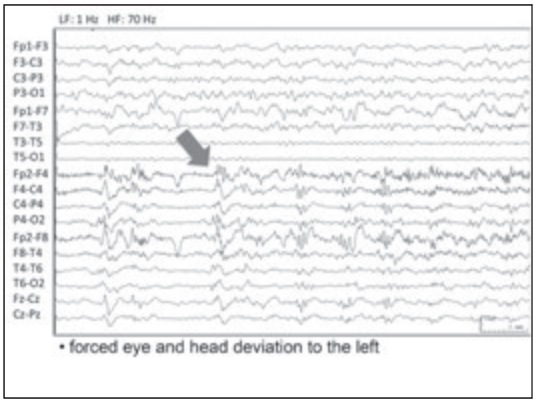
Kaplan. Epilepsia 2007; 48 (Suppl. 8): 39-41



- 95-year-old woman, right-sided chronic subdural hematoma



• forced eye and head deviation to the left

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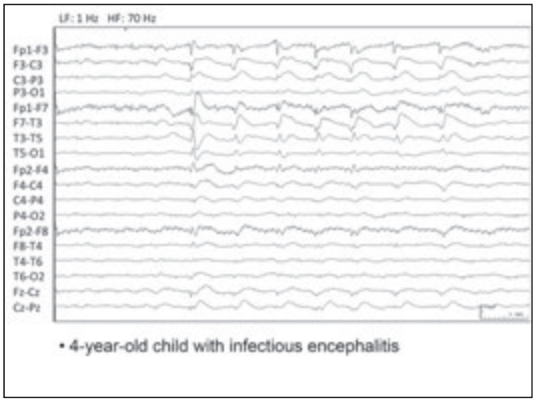
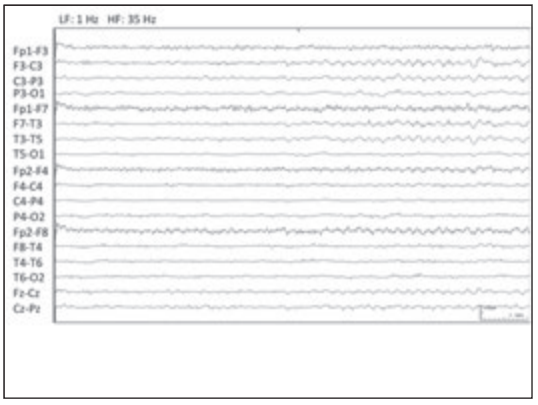
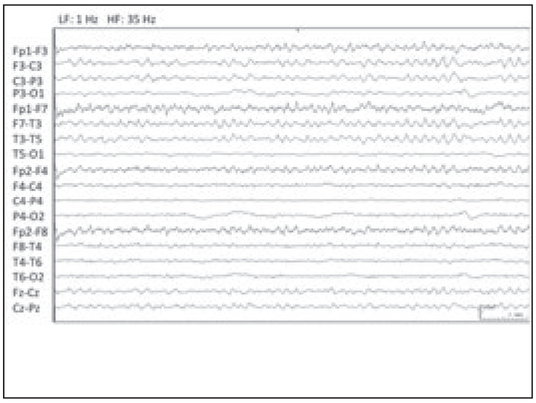


• 4-year-old child with infectious encephalitis

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F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
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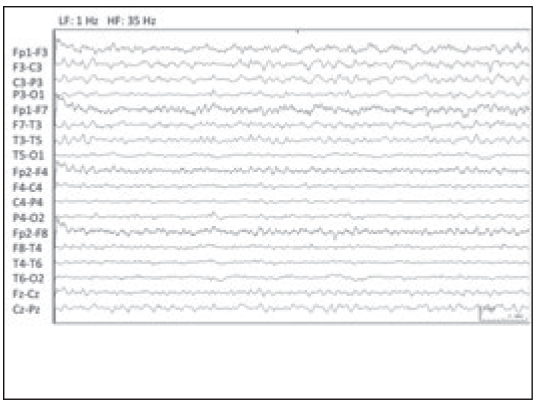
T4-T6
T6-O2
Fz-Cz
Cz-Pz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F3-C3
C3-P3
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F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
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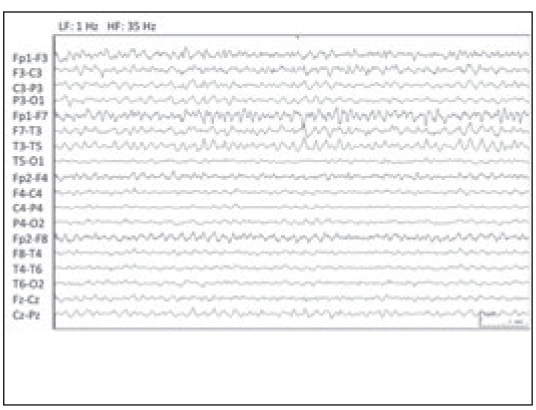
T4-T6
T6-O2
Fz-Cz
Cz-Pz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F3-C3
C3-P3
P3-O1
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F7-T3
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T5-O1
Fp2-F4
F4-C4
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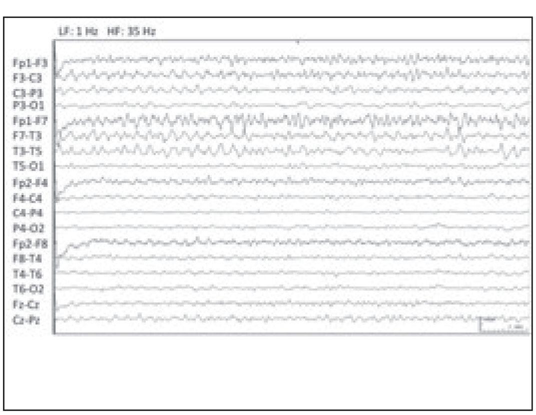
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C3-P3
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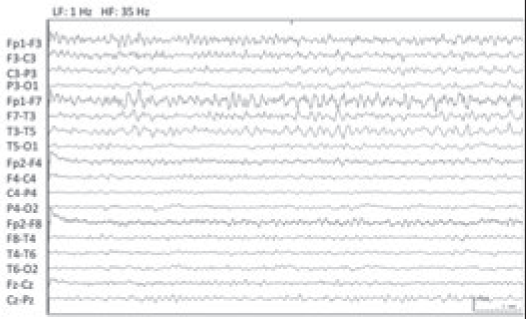
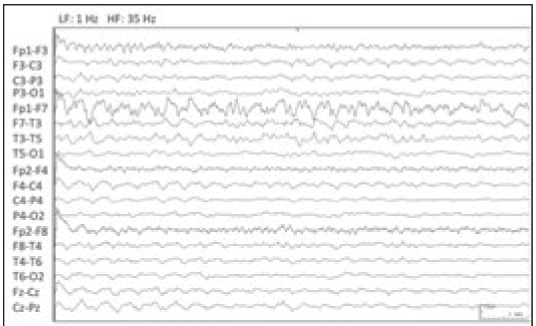
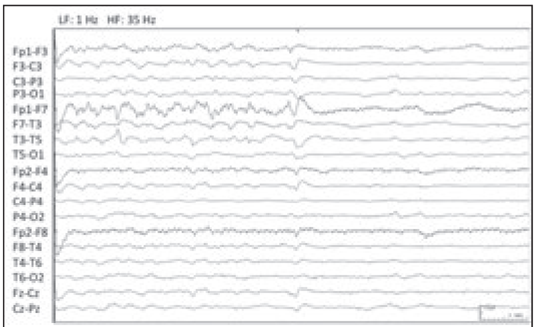
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz







Is nonconvulsive status epilepticus frequent in critically ill patients?

NEUROLOGY

Prevalence of nonconvulsive status epilepticus in comatose patients

A.B. Towne, MD, E.J. Waterhouse, MD, J.G. Boggs, MD, L.K. Garnett, RN, MS, A.J. Brown, R EEG T, J.R. Smith, Jr., BSEE, and R.J. DeLorenzo, MD, PhD, MPH

236 patients

- **admitted to ICU**
- **coma**
- **no signs of seizures**
- **EEG record of ≥ 30 minutes**

Towne et al. Neurology 2000; 54: 340-45

NEUROLOGY

Prevalence of nonconvulsive status epilepticus in comatose patients

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236 patients

- **admitted to ICU**
- **coma**
- **no signs of seizures**
- **EEG record of ≥ 30 minutes**

⇨ 19 (8%): nonconvulsive status epilepticus

Towne et al. Neurology 2000; 54: 340-45

	Seizures		Status Epilepticus	
Non neurologic ICU patients	4-15%	Oddo et al., 2009 Bleck et al., 1993	0.4%	Bleck et al., 1993
Stroke	5%	Lossius et al., 2002	1-10%	Velioğlu et al., 2001 Labovitz et al., 2001
Subarachnoidal hemorrhage	4-16%	Claassen et al., 2003 Hart et al., 2011 Olafsson et al., 2000 Rosengart et al., 2007	10-14%	Claassen et al., 2006 Hirsch et al., 2004
Intracerebral hemorrhage	10-30%	Kilpatrick et al., 1990 Passero et al., 2002 Sung et al., 1989 Bateman et al., 2007	1-21%	Sung et al., 1989 Bateman et al., 2007 De Reuck et al., 2007
Hypoxic-ischemic encephalopathy	5-40%	Krumholz et al., 1988 Levy et al., 1985 Snyder et al., 1980 Zandbergen et al., 2006	30%	Rossetti et al., 2009
Traumatic brain injury	12-50%	Englander et al., 2003	8-35%	Vespa et al., 2007 Temkin et al., 1990 Hirsch et al., 2004

Sutter et al. Crit Care Med 2013; 54: 1124-32

Persistent Nonconvulsive Status Epilepticus After the Control of Convulsive Status Epilepticus

- 164 with convulsive status epilepticus
- continuous EEG after initial treatment and control of convulsive seizures

DeLorenzo et al. Epilepsia, 1998

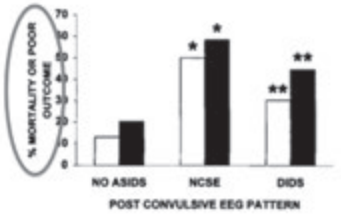
Persistent Nonconvulsive Status Epilepticus After the Control of Convulsive Status Epilepticus

- 164 with convulsive status epilepticus
- continuous EEG after initial treatment and control of convulsive seizures

- 52%: no post-SE epileptiform discharges
- 48%: persistent electrographic seizures
- ✧ 14%: nonconvulsive status epilepticus

DeLorenzo et al. Epilepsia, 1998

Persistent Nonconvulsive Status Epilepticus After the Control of Convulsive Status Epilepticus



DeLorenzo et al. Epilepsia, 1998

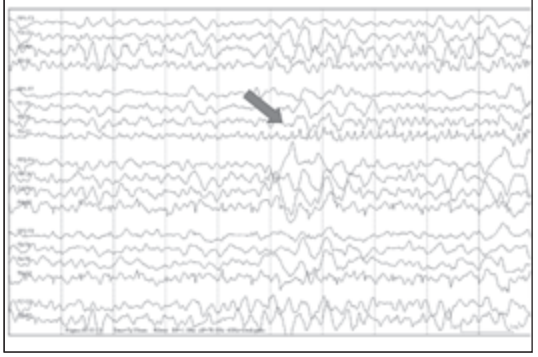
When should ongoing seizure activity be suspected?

- ✓ prolonged encephalopathy following generalized convulsions, an operative procedure, or a neurologic insult
- ✓ acutely impaired consciousness or fluctuating consciousness interrupted by normal alertness
- ✓ impaired mentation or consciousness with facial myoclonus or nystagmus
- ✓ episodic staring, aphasia, or automatisms
- ✓ other acutely altered behavior without obvious etiology

When should ongoing seizure activity be suspected?

- ✓ 6-year-old boy
- ✓ viral encephalitis
- ✓ convulsive status epilepticus, treated with Phenytoin and continuous IV Midazolam
- ✓ after tapering of IV drugs: episodes of altered behavior

When should ongoing seizure activity be suspected?



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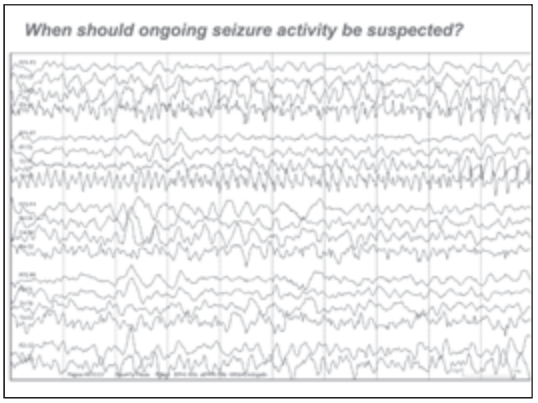

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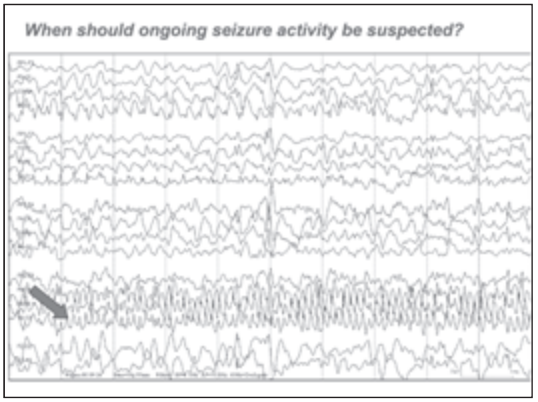

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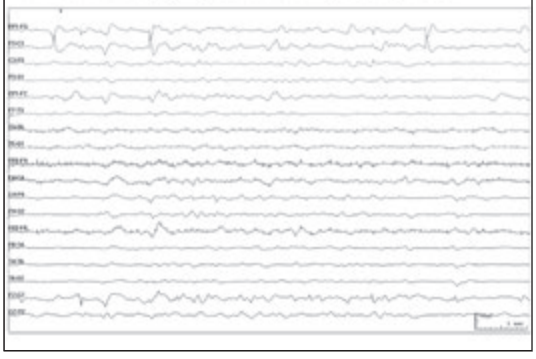
- ✓ episodic staring, aphasia, or automatisms
- ✓ other acutely altered behavior without obvious etiology

- ✓ encephalopathic patients with history of epilepsy or remote symptomatic brain lesions
- ✓ periodic interictal EEG patterns

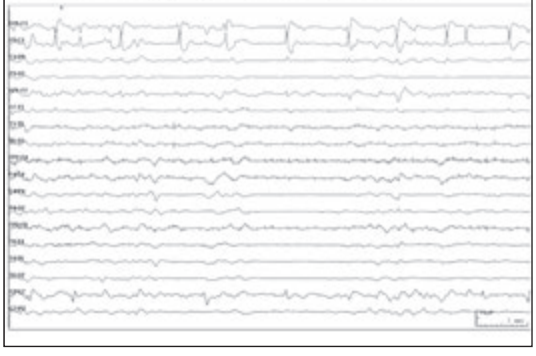
When should ongoing seizure activity be suspected?

- ✓ 89-year-old man
- ✓ previous stroke, dementia, chronic renal failure
- ✓ admitted due to respiratory infection
- ✓ convulsion, treated with IV Diazepam
- ✓ altered mental status

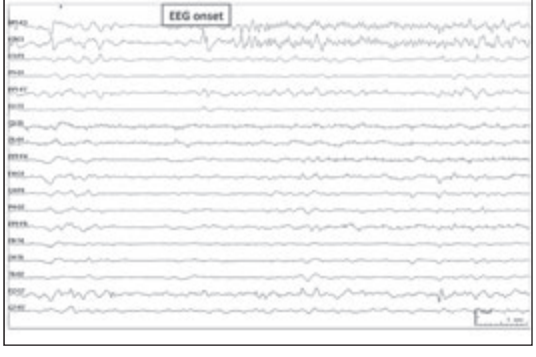
When should ongoing seizure activity be suspected?



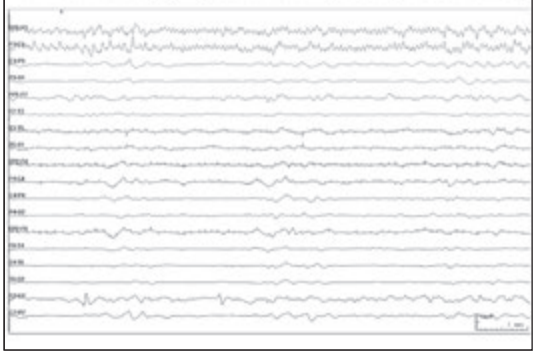
When should ongoing seizure activity be suspected?



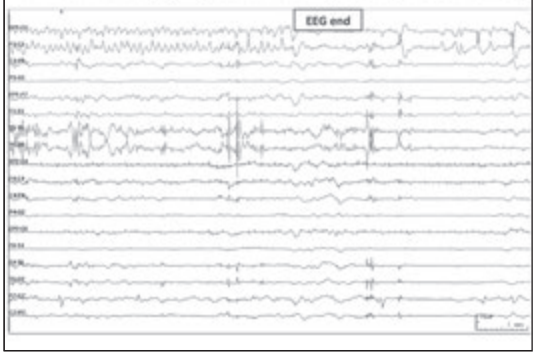
When should ongoing seizure activity be suspected? cEEG



When should ongoing seizure activity be suspected? cEEG



When should ongoing seizure activity be suspected? cEEG



We know that…

- ✓ it is important to recognize seizures (including nonconvulsive) in ICU patients

ONE

Acute seizures after intracerebral hemorrhage

A factor in progressive midline shift and outcome

P.M. Vespa, MD, K. O'Phelan, MD, M. Shah, MD, J. Mirabelli, MD, S. Starkman, MD, C. Kidwell, MD, J. Saver, MD, M.R. Nuwer, MD, J.G. Frazee, MD, D.A. McArthur, PhD, and N.A. Martin, MD

- ✓ 109 patients
  - 46 – ischemic stroke
  - 63 – intraparenchymal hemorrhage
- ✓ prospective cEEG monitoring
- ✓ CT at admission and 24, 48 and 72 hours ⇨ assessment of hemorrhage volume and midline shift
- ❖ all patients with ICH: prophylactic PHT (14-18 μg/ml)

Vespa et al. Neurology 2003; 60: 1441-6

CME

Acute seizures after intracerebral hemorrhage

A factor in progressive midline shift and outcome

P.M. Vespa, MD, K. O'Phelan, MD, M. Shah, MD, J. Mirabelli, MD, S. Starkman, MD, C. Kidwell, MD, J. Saver, MD, M.R. Nuwer, MD, J.G. Frazee, MD, D.A. McArthur, PhD, and N.A. Martin, MD

- ✓ Seizures during the first 72 hours:
  - 3/46 (6%) of patients with ischemic stroke
  - 18/63 (28%) of patients with ICH
- ✓ 16 patients: only electrographic seizures (nonconvulsive seizures)
- ✓ clinically: nonresponsive to commands, no overt motor signs

Vespa et al. Neurology 2003; 60: 1441-6

CME

Acute seizures after intracerebral hemorrhage

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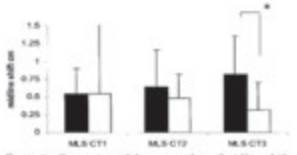


Figure 3. Comparison of the mean values of midline shift between patients with intracerebral hemorrhage with (black) and without (white) seizures on successive CT scans at 6, 24, and 48 to 72 hours.

Vespa et al. Neurology 2003; 60: 1441-6

CME

Acute seizures after intracerebral hemorrhage

A factor in progressive midline shift and outcome

P.M. Vespa, MD, K. O'Phelan, MD, M. Shah, MD, J. Mirabelli, MD, S. Starkman, MD, C. Kidwell, MD, J. Saver, MD, M.R. Nuwer, MD, J.G. Frazee, MD, D.A. McArthur, PhD, and N.A. Martin, MD

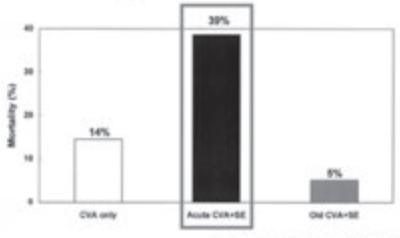
Neurologic deterioration in the first 72 hours ⇨ greater in the seizure cohort

	NIHSS at admission	NIHSS 72 hours
ICH + seizure	**14,8 ± 5,8**	**18,6 ± 6,1**
ICH without seizure	16,9 ± 8,5	17,7 ± 8,0

Vespa et al. Neurology 2003; 60: 1441-6

Synergistic effect of status epilepticus and ischemic brain injury on mortality

E.J. Waterhouse [a,*], J.K. Vaughan [a], T.Y. Barnes [b], J.G. Boggs [a], A.R. Towne [a], L. Kopec-Garnett [a], R.J. DeLorenzo [a]



Waterhouse et al. Epilepsy Res 1998; 29: 175-183

We know that…

- ✓ it is important to recognize seizures (including nonconvulsive) in ICU patients
- ✓ nonconvulsive seizures may damage the brain

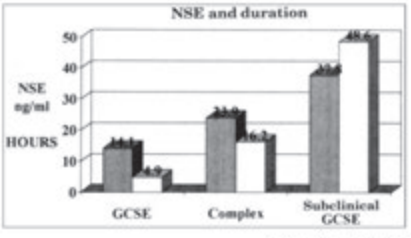
Complex partial status epilepticus accompanied by serious morbidity and mortality

Pt	Age/Sex	Seizure type	Status type (duration)	Previous seizures	Etiology	Neurologic deficit	Outcome
1	51/F	CPS, GTC	CPSE (36 hr)	Yes	Epilepsy	Severe retrograde amnesia	Permanent deficit
2	21/F	CPS, GTC	CPSE (72 hr)	Yes	Epilepsy	Mild to moderate cognitive and memory loss	Persistent deficit*
3	30/F	CPS, GTC	CPSE (36 hr)	Yes	Epilepsy	Memory and cognitive loss	Persistent deficit*
4	73/M	CPS	CPSE (48 hr)	No	Vascular	Severe cognitive and motor loss	Permanent deficit
5	63/F	CPS	CPSE (72 hr)	No	Vascular	Cognitive and motor loss	Permanent deficit
6	26/F	CPS, GTC	CPSE (72 hr)	No	Viral encephalitis	Moderate memory deficit	Permanent deficit
7	47/F	CPS, GTC, SP	CPSE (48 hr)	No	Encephalitis	Moderate/severe cognitive and motor loss	Death
8	41/M	CPS, GTC	CPSE (>72 hr)	No	Chronic renal failure and HIV	Moderate memory and cognitive loss	Persistent deficit*
9	82/F	CPS, GTC	CPSE (36 hr)	No	Unknown	Severe cognitive loss	Death
10	68/F	CPS	CPSE (48 hr)	No	Unknown	Coma and stupor	Death

Krumholtz et al. Neurology 1995; 45: 1499-504

Serum neuron-specific enolase in the major subtypes of status epilepticus

DeGiorgio C, Heck C, Rabinowicz A, Gott P, Smith T, Correale J



De Giorgio et al. Neurology 1999; 52: 746-9

Electrographic status epilepticus and long-term outcome in critically ill children

Katherine L. Wagenman, RN
Taylor P. Blake, MS
Sarah M. Sanchez, BA
Maria T. Schaibley, PhD
Jocelyne Rudolfo, PhD
Robert A. Berg, MD
Dennis J. Dlugos, MD, MSCE
Alexis A. Topjian, MD, MSCE
Nicholas S. Abend, MD

Objective Electrographic seizures (ES) and electrographic status epilepticus (ESE) are common in children in the pediatric intensive care unit (PICU) with acute neurologic conditions. We aimed to determine whether ES or ESE was associated with worse long-term outcomes.

Methods Three hundred children with an acute neurologic condition and encephalopathy underwent clinically indicated EEG monitoring and were enrolled in a prospective observational study. We aimed to obtain follow-up data from 137 subjects who were neurodevelopmentally normal before PICU admission.

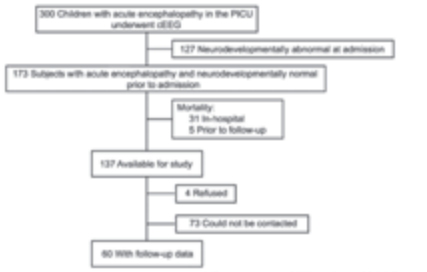
Results Follow-up data were collected for 60 of 137 subjects (44%) at a median of 2.7 years. Subjects with and without follow-up data were similar in clinical characteristics during the PICU admission. Among subjects with follow-up data, ES occurred in 12 subjects (20%) and ESE occurred in 14 subjects (23%). Multivariable analysis indicated that ESE was associated with an increased risk of unfavorable Glasgow Outcome Scale (Extended Pediatric Version) category (odds ratio 6.36, $p = 0.01$) and lower Pediatric Quality of Life Inventory scores (23 points lower, $p = 0.002$). Among subjects without prior epilepsy diagnoses ESE was associated with an increased risk of subsequently diagnosed epilepsy (odds ratio 13.3, $p = 0.002$). ES were not associated with worse outcomes.

Conclusions Among children with acute neurologic disorders who were reported to be neurodevelopmentally normal before PICU admission, ESE but not ES was associated with an increased risk of unfavorable global outcome, lower health-related quality of life scores, and an increased risk of subsequently diagnosed epilepsy even after adjusting for neurologic disorder category, EEG background category, and age. *Neurology®* 2014;83:1-9

Wagenman et al. Neurology 2014; in press.

Electrographic status epilepticus and long-term outcome in critically ill children

Figure Study flowchart



Wagenman et al. Neurology 2014; in press.

Electrographic status epilepticus and long-term outcome in critically ill children

60 patients with follow-up data

- ✓ Electrographic seizures (ES): 12 (20%)
- ✓ Electrographic status epilepticus (ESE): 14 (23%)

ES were not associated with worse outcomes

However, ESE was associated with:

- ✓ increased risk of unfavorable Glasgow Outcome Scale
- ✓ lower Pediatric Quality of Life Inventory scores
- ✓ increased risk of subsequently diagnosed epilepsy
  - ❖ *even after adjusting for neurologic disorder category, EEG background category, and age*

Wagenman et al. Neurology 2014; in press.

We know that…

- ✓ it is important to recognize seizures (including nonconvulsive) in ICU patients
- ✓ nonconvulsive seizures may damage the brain
- ✓ poor outcomes in critically ill patients with nonconvulsive seizures and nonconvulsive SE are affected by factors other than treatment
  - age
  - etiology
  - length of ICU stay (with its infectious complications)

But we don't know…

- ✓ If nonconvulsive seizures and nonconvulsive SE must be treated as aggresively as the convulsive varieties

Nonconvulsive seizures

❖ non sedative drugs are preferred

- Phenytoin
- Valproate
- Levetiracetam
- Orally administered drugs

Nonconvulsive status epilepticus

❖ often requires use of continuous IV anesthetic agent

- Midazolam
- Propofol
- Pentobarbital/Tiopental

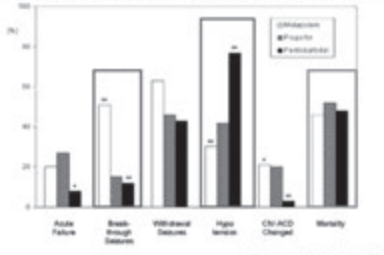
But we don't know…

- ✓ If nonconvulsive seizures and nonconvulsive SE must be treated as aggresively as the convulsive varieties
- ✓ Which anesthetic drug should be used

MIDAZOLAM	PROPOFOL	PENTOBARBITAL
✓ more breakthrough seizures ✓ increased risk of post treatment seizures	✓ shorter half-life ✓ safer than long-acting barbiturates ✓ risk of PRIS ❖metabolic acidosis, cardiac failure, rhabdomyolysis ❖prolonged infusion (>48hs) at more than 5 mg/kg/h	✓ more effective in preventing breakthrough seizures ✓ frequently complicated by hypotension

Treatment of Refractory Status Epilepticus with Pentobarbital, Propofol, or Midazolam: A Systematic Review

*†Ian Claassen, †Lawrence J. Hirsch, †Ronald G. Emerson, and *Stephan A. Mayer

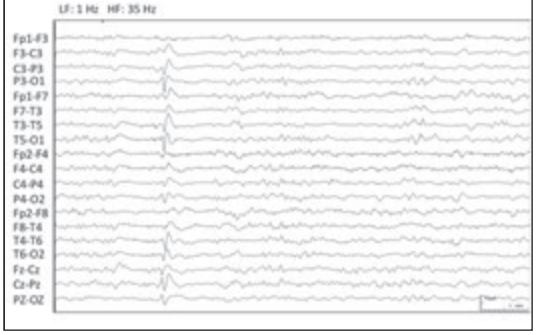


Claassen et al. Epilepsia 2002; 43: 146-53

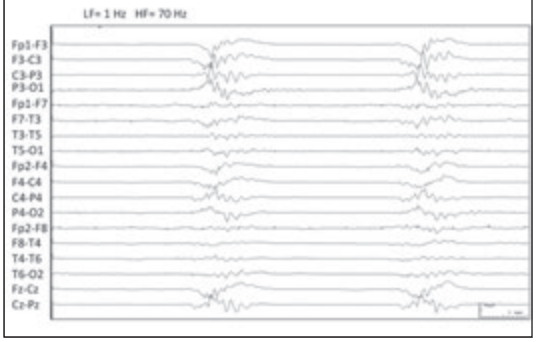
But we don't know…

- ✓ If nonconvulsive seizures and nonconvulsive SE must be treated as aggresively as the convulsive varieties
- ✓ Which anesthetic drug should be used
- ✓ Which should be the titration

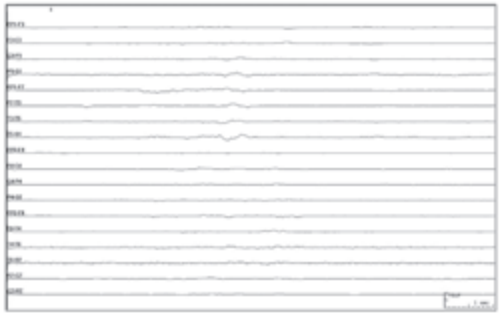
Suppression of seizures?



Burst-suppression?



Flat EEG?



In Nonconvulsive Status Epilepticus (NCSE), Treat to Burst-Suppression: Pro and Con

PRO	CON
Synergy * NCSE and acute brain injury	* do nonconvulsive seizures cause permanent brain injury?
Emergency * duration of NCSE predicts mortality	• treatment should not be more dangerous than seizures
Strategy * effectiveness	* etiology predicts mortality

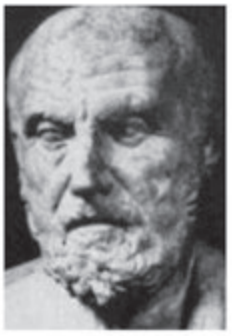
Jordan e Hirsch. Epilepsia 2006; 47 (Suppl 1): 41-45

NONCONVULSIVE SE IN CRITICALLY ILL PATIENTS

What do we need to know better?

- ✓ How aggressive should be the treatment of nonconvulsive seizures and nonconvulsive SE
- ✓ Which sedative agents should be used
- ✓ Which is the titration endpoint of anesthesic drip
- ✓ How should be the tapering of anesthetic drugs

❖ *Should we use sedative agents AT ALL?*



PRIMUM NON NOCERE

Anesthetic drugs in status epilepticus: Risk or rescue?

A 6-year cohort study

Raoul Sutter, MD
Stephan Marsch, MD, PhD
Peter Fuhr, MD
Peter W. Kaplan, MB, BS, FRCP
Stephan Rüegg, MD

ABSTRACT

Objective: To evaluate the risks of continuously administered IV anesthetic drugs (IVADs) on the outcome of adult patients with status epilepticus (SE).

Methods: All intensive care unit patients with SE from 2005 to 2013 at a tertiary academic medical care center were included. Relative risks were calculated for the primary outcome measures of seizure control, Glasgow Outcome Scale score at discharge, and death. Poisson regression models were used to control for possible confounders and to assess effect modification.

Results: Of 171 patients, 37% were treated with IVADs. Mortality was 18%. Patients with anesthetic drugs had more infections during SE (63% vs 11%, $p < 0.0001$) and a 2.9-fold relative risk for death (2.88, 95% confidence interval 1.45–5.73), independent of possible confounders (i.e., duration and severity of SE, nonanesthetic third-line antiepileptic drugs, and critical medical conditions) and without significant effect modification by different grades of SE severity and etiologies. As IVADs were used after first- and second-line drugs failed, there was a correlation between treatment refractory SE and the use of IVADs, leading to insignificant results regarding the risk of IVADs and outcome after additional adjustment for refractory SE.

Conclusions: Our findings heighten awareness regarding adverse effects of IVADs. Randomized controlled trials are needed to further clarify the association of IVADs with outcome in patients with SE.

Classification of evidence: This study provides Class III evidence that patients with SE receiving IVADs have a higher proportion of infection and an increased risk of death as compared to patients not receiving IVADs. *Neurology*® 2014;83:1–9

Sutter et al. Neurology 2014; in press.

Anesthetic drugs in status epilepticus: Risk or rescue?

A 6-year cohort study

- ✓ 171 patients with SE
  - ❖ 50 patients: nonconvulsive SE in coma
- ✓ 37%: treated with IV anesthetic drugs

Sutter et al. Neurology 2014; in press.

Anesthetic drugs in status epilepticus: Risk or rescue?

A 6-year cohort study

Patients with anesthetic drugs:

- ✓ had more infections during SE
- ✓ had a 2.9-fold relative risk for death
  - ❖ independent of possible confounders (duration and severity of SE, nonanesthetic third-line antiepileptic drugs, and critical medical conditions)
  - ❖ without significant effect modification by different grades of SE severity and etiologies

Sutter et al. Neurology 2014; in press.

"If we doctors threw all our medicines into the sea, it would be that much better for our patients and that much worse for the fishes."

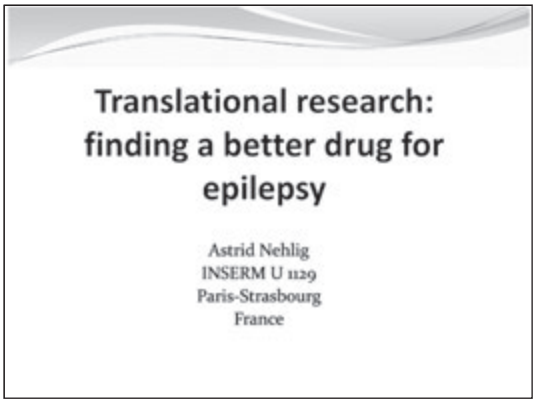
MUITO OBRIGADO

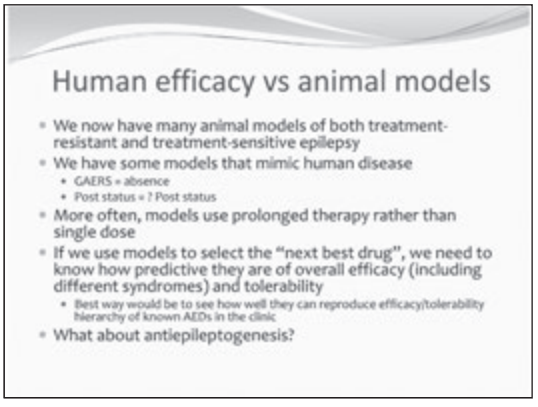
MUCHAS GRACIAS

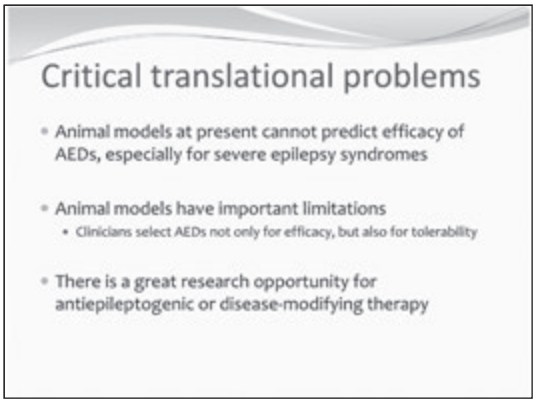
THANK YOU VERY MUCH

Astrid Nehlig (France)

TRANSLATIONAL RESEARCH: FINDING A BETTER DRUG FOR EPILEPSY



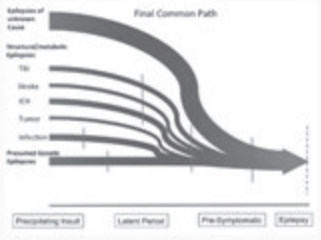




Epileptogenesis: definitions

- **Epileptogenesis**: the development and extension of tissue capable of generating spontaneous seizures, resulting in
  - development of an epileptic condition and/or
  - progression after the condition is established
- **Disease-modification**:
  - anti-epileptogenesis (AEG) and co-morbidity modification
- **Anti-epileptogenesis (AEG) treatments** (prior to or after epilepsy onset)
  - **Prior** to epilepsy onset: prevent or delay the development of epilepsy (if seizures occur, they may be fewer in frequency, shorter, or of milder severity)
  - **After** the diagnosis of epilepsy: alleviate seizure severity, prevent or reduce epilepsy progression, change seizures from drug-resistant to drug-sensitive
- **Comorbidity-modifying treatments**
  - alleviate or reverse the symptomatic development or progression of epilepsy-related co-morbidities.
- **Cure**: a complete and permanent reversal of epilepsy (no seizures after treatment withdrawal).

Variable timing for AEG therapy



French et al., 2013

Results of preclinical and clinical studies

- Clinical trials of anti-seizure drugs as AEGs have been negative (*Temkin, 2009*):
  - problems with trial designs
  - anti-seizure drugs are not designed or selected to have AEG activity
    - → importance of focused AEG strategies
- Some proof-of-concept experimental studies have shown positive treatment effects on epileptogenesis (*Pitkänen & Lukasiuk, 2011; François et al., 2009*) but they are limited and so far, none has progressed to clinical investigations

Critical technical and methodological issues for preclinical trials

Design of AEG preclinical studies

- Study-design
  - blinded, placebo-controlled, statistically powered
- Animals
  - rats (either gender)
- Experimental model
  - selection of a model appropriate for the syndrome targeted by the tested treatment
- Timing, dosing and duration of treatment
  - based on target relevance (if target is known)
  - evidence for exposure and engagement of the target by the treatment should be provided
- Outcome measures
  - primary outcome measures: seizure frequency; percentage of animals seizure free during the period of seizure monitoring
  - secondary outcome measures: seizure duration; seizure type
- Statistics
  - predefined; inclusion of statistician into the team from the beginning
- Reporting
  - both positive and negative outcome

Pitkanen et al., 2013

Should drugs be tested in more than one species?

- Poor predictability: about 30% of toxic side effects occurring in humans cannot be predicted by testing in any species
  - species differences in absorption, distribution, metabolism or excretion, PK, drug effects, etc…
  - regulatory agencies generally require toxicological testing in two species (one rodent, one non-rodent)
- Use of higher non-rodent species not clearly superior

Galanopoulou et al., 2013

Study design, toxicity, general methods

- Necessity to confirm that the drug crosses the BBB and reaches the intended target
  - Brain levels
  - Correlation between blood and brain levels?
- Toxicity studies
  - Is the drug tolerated in rodents?
  - Dose-response curve for efficacy and adverse effects
- Need for in vivo evidence that the compound changes the epilepsy phenotype

Galanopoulou et al., 2013

Drug formulation and delivery

- Purity
- Method, timing and clinical relevance of administration
- Identify the therapeutic dose and time window
- Vehicle composition
- Assess drug pharmacokinetics and pharmacodynamics
- Various delivery routes are used in animals
  - may be acceptable for preclinical studies of proof-of-concept
  - may not always be clinically applicable (e.g., intraperitoneal or intracerebral injections)
  - critical to demonstrate that a clinically relevant delivery method and treatment protocol is effective and well tolerated

Galanopoulou et al., 2013

Video-EEG monitoring

- Video-EEG recording appears mandatory
- What type of electrodes
  - Surface: sufficient to record occurrence of seizures
  - Unilateral vs bilateral
  - Location and number of channels
- Characterization of seizures
  - Quantitative behavioral and electrographic criteria used to define seizures
- Computational seizure detection
- Duration of recording
  - continuous EEG recording from the time of insult and as long as possible
  - recordings at later times may sometimes be sufficient

Galanopoulou et al., 2013

Monitoring other outcomes (tolerability)

- Minimal essential outcomes
  - Simple measures of toxicity
  - Failure to thrive: weight loss
- Model/treatment-specific and other outcomes
  - Physiology, imaging, electrophysiological and molecular tissue studies
  - Behavioral outcomes for comorbidity and CNS dysfunction

Galanopoulou et al., 2013

Behavioral studies to assess tolerability

BASIC BATTERY	
General appearance and condition	Lethality; Convulsions; Tail position (flat or Straub-tail); Sedation or excitation; Abdominal writhes
Thriving	Body weight
Physiologic functions	Defecation; Salivation; Urination; Respiration; Hypo or hyperthermia
Other systems	Whiskers: orientationg ;Fur: condition, piloerection Eyes: eyes open, red eyes, lacrimation, red tears
Behavior	Compulsive biting or licking, self-mutilation, aggressiveness, stereotypies, scratching, grooming Pick up test; Finger-snap test (fear, startle) Positional passivity test (tail holding test)
Motor, gait and stance	Gait; Locomotor activity, akinesia, tremors, jumps; head twitches, headflicking, head searching Limb and body tone; Grip traction, grasping; balance and motor coordination; rotarod
Pain sense	Tail pinch
Sensory	Positional sense testing

Galanopoulou et al., 2013

Behavioral studies to assess tolerability

OPTIONAL	
Social behavior	Nest building Social Chamber test
Motivation	Motivation test
Depression	Forced / helpless swimming test Tail suspension test
Learning and memory	Various mazes; New object recognition Passive and active avoidance Contextual fear conditioning LTP (in vitro)
Anxiety	Forced swim Elevated plus maze
Attention	Poke hole test
Reactivity to sensory stimuli	Approach response test; Touch response test Auditory startle

Galanopoulou et al., 2013

Behavioral studies to assess tolerability

General neurological exams	
Alertness	Transfer arousal
Motor and coordination (additional)	Grip-traction tests; Rotarod; Beamwalk Computerized home cage or open field activity Locomotor coordination test
Reflexes (additional)	Rooting reflex; Vibrissae placing; Forelimb placing; Postural, flexion, grasping and corneal reflex
Sensory (additional)	Limb-placing tests (visual, forelimb or forelimb-hindlimb sensory placing)

Galanopoulou et al., 2013

Specific requirements for preclinical antiepileptogenesis trials in immature animals

- Factors affecting target expression
- Different ratio between neurons and astrocytes
- Developmental differences in the expression and function of proteins, enzymes, receptors, ion channels, transporters, in rates of neurogenesis and apoptosis, and in the consequences of brain injury on these events
- Different resistance to changes in cell environment that may accompany seizures (e.g., hypoxia/anoxia)
- Shift from predominantly anaerobic to aerobic metabolism: progressive maturation of energy metabolism and compartmentation of glutamate metabolism
- Natural ketosis in immature rodents
- Age-related differences in the effects of seizures, precipitating events, and their treatments on the processes implicated in epileptogenesis

Galanopoulou et al., 2013; Pitkänen et al., 2013

Specific requirements for preclinical antiepileptogenesis trials in immature animals

- Factors affecting drug dosing and duration of treatment
  - Different permeability of the BBB and hence access to the brain
  - Different distribution within the brain (ratio lipids/water lower)
  - Different pharmacokinetics related to the immaturity of the hepatic enzymes of drug metabolism
- Factors affecting selection and interpretation of outcome measures
  - EEG recordings may not be possible especially in newborn mice due to size and fragility of skull.
  - Prolonged classical video-EEG recordings on the same animal are not possible in developing animals due to growing size of skull/brain and the need for the pups to be cared by the dam
  - Alternative solutions may affect the design of study, power analysis, and interpretation of results
  - Developmental differences in connectivity and function of cortical and subcortical networks involved in seizures and their control
  - Age-specific expression of early life seizures or developmental differences in the evolution of the phenotype of early life epileptic syndromes may need to be accounted for in the design and interpretation of AEG studies in immature animals

BASIC BEHAVIORAL BATTERY FOR TOLERABILITY	IN IMMATURE ANIMALS
Neurodevelopmental reflexes (<1 min/day/rodent)	Surface righting time (daily); Open field activity (age-adapted; daily); Negative geotaxis (daily); Horizontal bar (daily)

Galanopoulou et al., 2013; Pitkänen et al., 2013

Non pharmacological treatment therapies: Gene therapy

- Adeno-associated virus (AAV), lentivirus, and herpes simplex virus: advantageous translational potential
- Potential consequences
  - Problems linked to the distribution of the transgene in the brain
  - Inflammatory response linked to the viral injection
  - Overexpression of the transgene
  - Tumorigenesis caused by transgene transduction
  - Behavioral side effects

Galanopoulou et al., 2013

Non pharmacological treatment therapies: Cell and stem cell therapies

- Embryonic stem, cord blood, inducible pluripotent stem and induced neuronal cells
- Same controls as for gene therapy plus
  - degree of survival and distribution/migration of the grafted cells in the brain
  - phenotype of the cells, neuronal properties, and synaptic integration into the host circuitry
  - the long-term stability of the neuronal phenotype

Galanopoulou et al., 2013

Non pharmacological treatment therapies: DBS, KD, herbal medicines

- Deep brain stimulation
  - electrode localization
  - possible inflammatory response
  - variety of stimulation paradigms including the brain region
  - EEG monitoring
  - Efficacy, long-term and side effects in relevant models
- KD and herbal medicine
  - KD: study of changes in metabolism, EEG and side effects
  - Herbs: complement or replace traditional drugs, same degree of control needed

Galanopoulou et al., 2013

How to decide which drugs should enter "phase II" preclinical development

Suggested solution: a multi-step approach

Pitkanen et al., 2013

Decision point 1

criteria to enter "phase II" pre-clinical development

- Data on clinically relevant endpoints
- Degree of improvement (size of the effect)
  - positive (therapeutic) evidence prevails over negative/toxicity evidence at this stage
- Data replicated in an independent laboratory
- Positive data in more than one model/species
  - how many models are available for the syndrome targeted: e.g. if only one model available, positive data in that model may be sufficient;
  - if a therapy is effective in more than one model, then its value is increased
- Data published in high quality peer-reviewed journals.

O'Brien et al., 2013

Decision point 1

criteria to enter "phase II" pre-clinical development

- Replication
  - not all animal models are ideal for phase II
  - exact replication can be difficult and most studies do not replicate
  - if findings depend on specific experimental conditions, they are unlikely to be of immediate clinical relevance and further development is necessary
- PK and toxicology data
  - not strictly needed for access to Stage II studies
  - PK and toxicology data are generally not available early in discovery
  - PK and toxicology studies could be additional services to help in development of promising compounds - partnership with the pharmaceutical industry

O'Brien et al., 2013

Preclinical trial: goals

- Generating more rigorous pre-clinical efficacy data to address current gaps in epilepsy treatment (i.e. drug resistant seizures, anti-epileptogenesis, disease modification or co-morbidities)
- De-risk clinical development, enhancing the attractiveness of funders (industry and government) to invest in the clinical development of potential new drugs

O'Brien et al., 2013

Preclinical trials:

organization of the study

- Multi-center studies designed along the lines of Phase II/III clinical studies
- Primary endpoints relate to efficacy
  - but may include some toxicity and pharmacokinetic assessments
- Standardized methods and endpoints, rigorous statistical and sample size calculations, rigorous blinding, independent data monitoring and analysis
- In total, a large number of animals (divided between many centers)
  - number of laboratories involved: 5-20
  - number of animals per study: based on power calculation from proof of concept studies (likely 40-200)

O'Brien et al., 2013

Preclinical trial:
organization of the study

- A central coordinating site for each study independent from the data collections sites
  - data collected at individual sites could be blindly analyzed partly by the local sites for relevant endpoints (e.g. seizure quantification, neurobehavioural testing)
  - raw and/or analyzed data transmitted to the central coordinating site for higher level analysis and pooling with data from other sites for the final data analysis
  - independent monitoring of data collection and analysis, as with clinical trials

O'Brien et al., 2013

Preclinical trial:
translatability

- Translatability should be addressed in phase II pre-clinical studies
  - there is often a significant lack of parallel between the models and the clinical condition that they are expected to model: phase II studies should employ the best possible models
  - failed human trials may reflect insufficient understanding of the conditions necessary for the candidate therapy to work (for example: delivery forms, PK, dosing): phase II studies should include these aspects

O'Brien et al., 2013

Preclinical trial:
selection of participating laboratories

- Done by the central coordinating site from the database of laboratories that have volunteered to be involved in phase II studies.
- Selection criteria
  - track record of high quality pre-clinical studies, evidenced by peer-reviewed publications, record of previous participation in phase II studies, possibly site inspection
  - availability and experience in the animal models selected to utilized for the study
  - capacity to undertake the required number of studies within current workload (estimated 10-20 animals in 1-3 models)
  - capacity to store and account for the drug under investigation
  - no significant conflicts of interest

O'Brien et al., 2013

Preclinical trial: funding

- Phase II multicenter pre-clinical studies will be expensive, resource and time intensive
  - However, significantly less that of failed Phase II/III clinical studies
- The funding model will likely require a combination of government funding and private grant funding
  - The basic IP for the compounds would remain with the "sponsor" of the compound
- Participating investigators would receive funds to cover the costs of studies and infrastructure

O'Brien et al., 2013

Statistics

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

Abstract | A study with low statistical power has a reduced chance of detecting a true effect, but it is less well appreciated that low power also reduces the likelihood that a statistically significant result reflects a true effect. Here, we show that the average statistical power of studies in the neurosciences is very low. The consequences of this include overestimates of effect size and low reproducibility of results. There are also ethical dimensions to this problem, as unreliable research is inefficient and wasteful. Improving reproducibility in neuroscience is a key priority and requires attention to well-established but often ignored methodological principles.

Nat Rev Neurosci 2013

Statistics

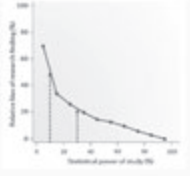
RECOMMENDATIONS FOR RESEARCHERS

- **Perform an a priori power calculation**
  - Estimate the size of effect you are looking for and design your study accordingly.
- **Disclose methods and findings transparently**
  - If the intended analyses produce null findings and you move on to explore your data in other ways, say so. Null findings locked in file drawers bias the literature, whereas exploratory analyses are only useful and valid if you acknowledge the caveats and limitations.
- **Pre-register your study protocol and analysis plan**
  - Pre-registration clarifies whether analyses are confirmatory or exploratory, encourages well-powered studies and reduces opportunities for non-transparent data mining and selective reporting. Various mechanisms for this exist (for example, the Open Science Framework).
- **Make study materials and data available**
  - Making research materials available will improve the quality of studies aimed at replicating and extending research findings. This will enhance opportunities for data aggregation and meta-analysis, and allow external checking of analyses and results.
- **Work collaboratively to increase power and replicate findings**
  - Combining data increases the total sample size (and therefore power) while minimizing labor and resource impact on any one contributor. Large-scale collaborative consortia in fields such as human genetic epidemiology have transformed the reliability of findings in these fields.

Statistics

Table 2 | **Sample size required to detect sex differences in water maze and radial maze performance**

	Total animals used	Required N per study		Typical N per study		Detectable effect for typical N	
		80% power	95% power	Mean	Median	80% power	95% power
Water maze	420	134	220	22	20	$d = 1.26$	$d = 1.62$
Radial maze	514	68	112	24	20	$d = 1.20$	$d = 1.54$



The median statistical power of studies in the neuroscience field is between ~8% and ~31%
⟹ potentially large bias in findings

Biomarkers for studies on anti-epileptogenesis: do we know when to intervene?

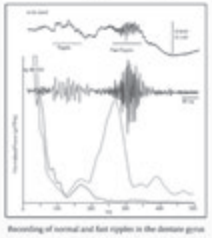
Pathological high frequency oscillations (pHFOs)

Pathological high frequency oscillations (pHFOs) or fast ripples (FR)

- These brief (15-30 ms) high frequency (250-500 Hz) oscillations are generated by local clusters of neurons pathologically interconnected
- Normal ripples can be recorded from the dentate gyrus
- pHFOs never occur under normal conditions
  - typically recorded interictally
  - uniquely associated with regions capable of generating spontaneous seizures
  - could reflect the basic neuronal events underlying epileptogenesis

Engel et al., 2009

Pathological high frequency oscillations (pHFOs)



Recording of normal and fast ripples in the dentate gyrus

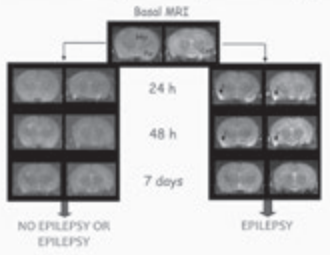
- pHFOs occur at the onset of ictal events in rodents, associated with mechanisms of seizure generation
- In rodents, FR-generating neurons are present in small clusters spatially stable over time
- In patients with TLE, strong association between occurrence of FRs and hippocampal atrophy on MRI
- pHFOs can be recorded shortly after intrahipp KA only in rats that develop spontaneous seizures
- Limitations: invasive technique needing depth electrode implantation

Engel et al., 2009

MRI studies after lithium-pilocarpine SE in immature rats

MRI in PN21 rats:

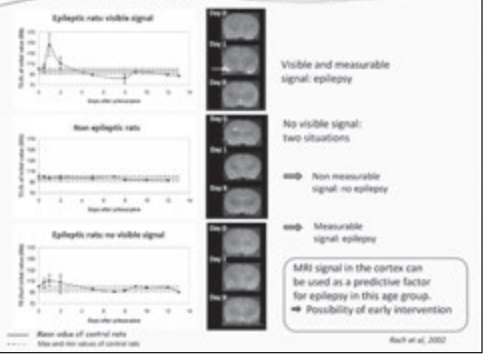
All PN21 rats develop SE but only 60% become epileptic



➢ The early signal in temporal cortices is predictive of epilepsy at this age

Rauh et al, 2002

T2 relaxometry in PN21 rats



Rauh et al, 2002

Conclusions

- Identifying new drugs for epilepsy and mainly those targeted at AEG will require a lot of drastic conditions:
  - Homogeneity of research procedures
  - Communication between groups
  - More sophisticated techniques and equipments
  - Larger groups of animals (statistics)
  - Intergroup reproducibility
  - Possibility of publishing both negative and positive results
  - Identification of new biomarkers

Thanks to

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- The International League Against Epilepsy Working Group on Recommendations for Preclinical Epilepsy Drug Discovery and the American Epilepsy Society Basic Science Committee:
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Bruce Hermann (USA)

NEUROPSYCHOLOGICAL AND BRAIN CHANGES IN AGING PERSONS WITH CHRONIC EPILEPSY

Aging and Epilepsy: Effects on Cognition, Brain and Behavior

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University of Wisconsin School of Medicine and Public Health
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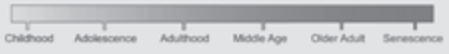
Overview

- Focus on comorbidities (cognition, psychiatric complications)
- Examine the nature, development, and course of these problems in epilepsy
- Take a broad life span perspective
- Start in middle age and look forward (progression) and then backward (origin)



Two questions

1. What is the status and trajectory of problematic cognition and brain structure in middle age and beyond?
2. Why and when do these issues develop?

Demographic and Clinical Characteristics

Characteristic	Controls (n=82)	TLE (n=96)
Age (y)	33.6	36.9
Gender (% F)	59.7	66.6
Years of education	13.6	13.0
Full-scale IQ	106.4	92.9
Duration of epilepsy (yrs)	—	21.6
Age at onset (yrs)	—	14.8

Age, education, onset, and duration are presented as means.

Neuropsychological Test Battery

Domain	Ability
Intelligence	Verbal Nonverbal
Language	Confrontation naming Verbal fluency
Visuoperceptual	Facial discrimination Spatial judgment
Verbal memory	Auditory memory–immediate Auditory memory–delayed
Nonverbal memory	Visual memory–immediate Visual memory–delayed
Executive function	Problem solving Response inhibition Speeded psychomotor Working memory
Motor	Speeded psychomotor Speeded fine motor dexterity

[1]raw scores, [2]perseverative responses, [3]seconds

Cognition in Chronic TLE

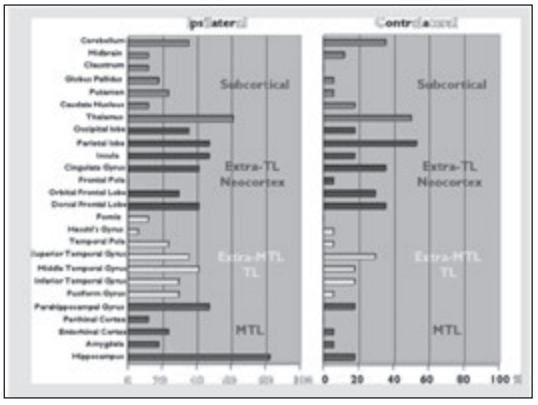
Cognitive Measures

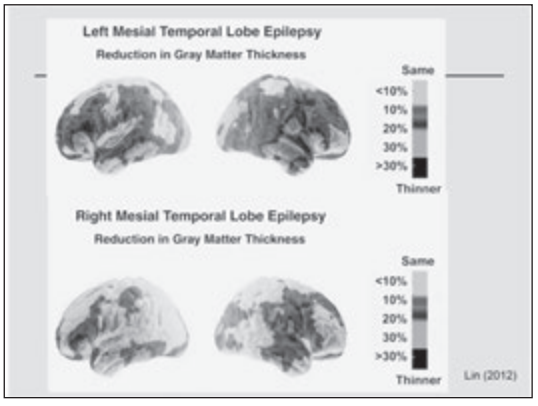
Oyegbile et al. (2004)

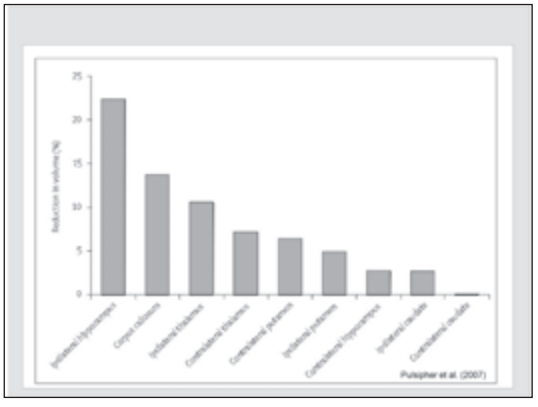
Cognition in Chronic TLE

Cognitive Measures

Oyegbile et al. (2004)







Lifetime to Date DSM-IV Diagnoses

	Controls (n=70)	TLE (n=52)
Axis I Disorder	**42.9%**	**75.0%***
Mood Disorders	**32.9%**	**51.9%****
Anxiety Disorders	22.9%	36.5%
Major Depression	**27.1%**	**42.3%*****

*p=.001, **p=.037, ***p=.019

Jones et al. (2005)

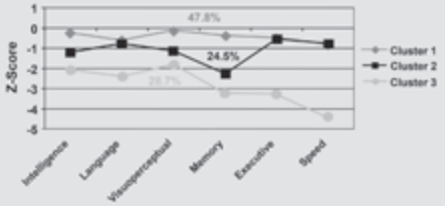
Cognition in Chronic TLE

Oyegbile et al. (2004)

Taxonomy of Cognition

- Similarity measure
  - Euclidean distance
- Hierarchical clustering procedure
  - Ward's Method
- Cognitive domains
  - Intelligence
  - Language
  - Visuoperceptual
  - Memory
  - Executive
  - Speed

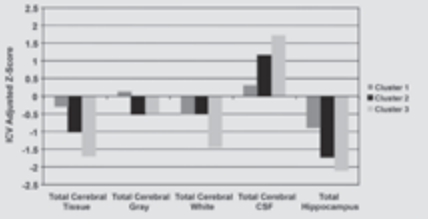
Cognitive Phenotypes

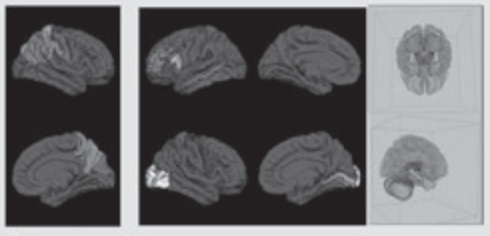


Demographic / Epilepsy Characteristics

	Cluster 1 (47.8%)	Cluster 2 (24.5%)	Cluster 3 (28.7%)
Age*	33.6	37.9	41.8
Gender (%F)	63.0	72.0	65.0
Education	13.4	13.1	12.4
Onset	15.5	15.6	12.9
Duration*	17.5	21.7	27.1
AEDs*	1.6	1.7	2.0

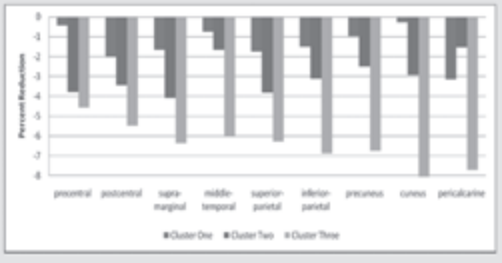
Volumetric Characteristics



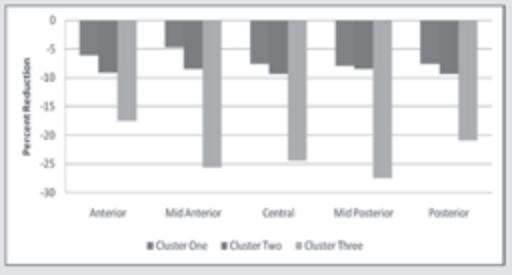


Bilateral effects | Unilateral effects | Subcortical and cerebellar

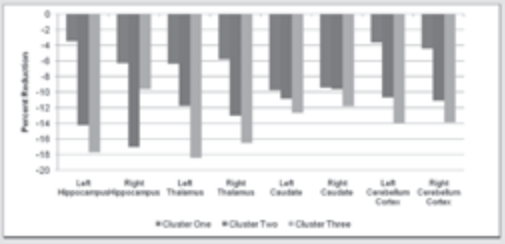
Cortical Thickness



Corpus Callosum Volumes



Subcortical/Cerebellar Volumes



Summary

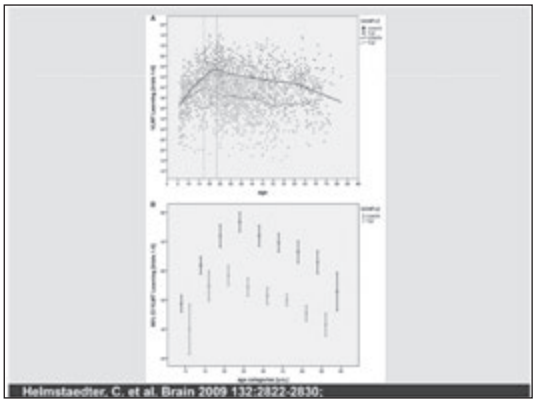
- Cognition is globally affected in chronic TLE
  - But there is an underlying taxonomy of cognitive morbidity
  - Poorest cognition associated with older age, longer duration, more AEDs, more volumetric abnormality
- Significant volumetric abnormalities
  - Extend beyond the primary epileptogenic region
  - Degree of abnormality related to cognitive pathology
  - Of clinical consequence

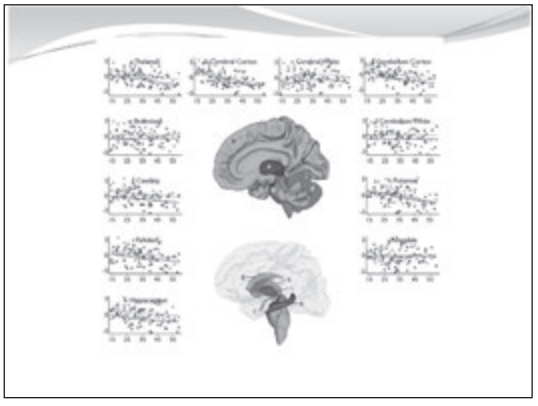
Life Span

Prospective Studies

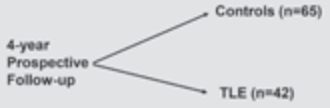
- Tested at least twice
  - 12+ studies of children with epilepsy
  - 13+ studies of adolescents / adults with epilepsy
- Span of investigations
  - First study—Fox (1928)
  - Latest study—Griffith et al. (2012)
- Cognitive declines occur in a subset of patients
- Typically among those with more severe epilepsy
  - eg, estimated lifetime GTC, status epilepticus

Dodrill (2004) , Seidenberg et al. (2007)


Helmstaedter, C. et al. Brain 2009 132:2822-2830;

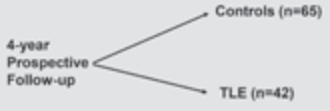


Prospective Follow-Up

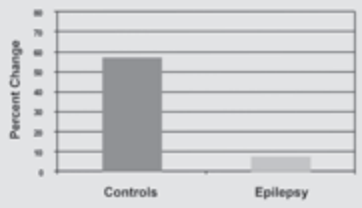


Prospective Follow-Up

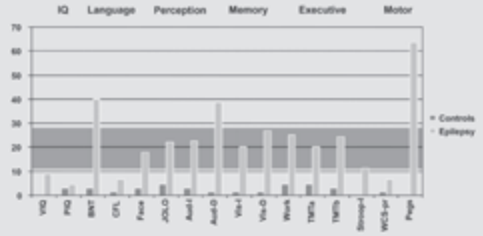
Cognitive Assessment
Psychiatric Interview
Quantitative MRI



Significant Test-Retest Improvements



Percent Abnormal Prospective Cognition



Predictor Variables

Age (yrs)
Education (yrs)
Baseline FSIQ

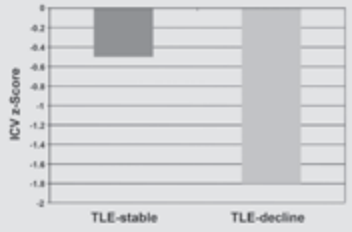
Onset (yrs)
Duration (yrs)
AEDs (number)

Baseline total gray matter (ICV-z)
Baseline total white matter (ICV-z)
Baseline total CSF (ICV-z)
Baseline left hippocampus (ICV-z)
Baseline right hippocampus (ICV-z)

Verbal Memory

	Stable	Decline
Age	32.5	37.5
Education	13.2	12.5
Baseline FSIQ	96.3	81.1
Onset	12.3	9.6
Duration	20.1	27.6
AEDs	1.7	2.1
Total gray matter	-.19	-.93
Total white matter	-.56	-1.02
Total CSF	.23	1.04
Left hippocampus	-.50	-1.8
Right hippocampus	-1.65	-1.69

Memory Change and Baseline Hippocampus



Predictors of Prospective Change

Strong Predictors

Baseline volumetric abnormalities (10)
Baseline IQ (5)
Duration (4)
Age (2)
Education (2)
Onset (1)
AEDs
Seizure frequency

Weak Predictors

Outcome Measures

- Neuropsychological prognosis
- Psychiatric prognosis
- Quantitative volumetric prognosis

Psychiatric Assessment

- Baseline standardized psychiatric interview (SCID)
- Re-interviewed (SCID) 4 years later to determine rate of interval Axis 1 disorders

Interval DSM-IV Diagnoses

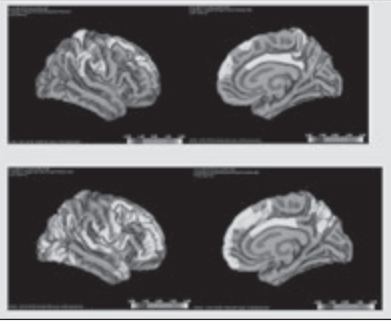
	Controls (n=70)	TLE (n=52)
Axis 1	21.4%	65.4%
Mood Disorders	17.5%	38.5%**
Anxiety Disorders	20.0%	34.6%*
Major Depressive Episodes	14.3%	25.0%

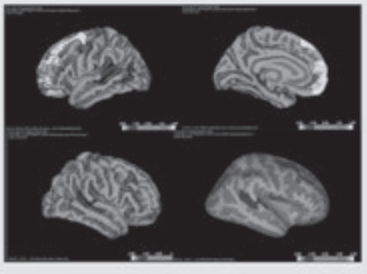
*P<.05
**P<.01
***P<.001

Jones et al. (2007)

Volumetric Outcomes

- Neuropsychological prognosis
- Psychiatric prognosis
- Quantitative volumetrics

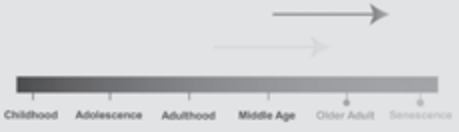




Progression Summary

- Cognitive progression—yes
  - In approximately 20%-25% of patients
  - In vulnerable cognitive domains
  - Predictors include demographic and clinical epilepsy characteristics as well as baseline volumetric abnormalities
- Psychiatric progression—yes
  - Increased rates of Axis 1 disorders, mood and anxiety disorders
- MRI progression—
  - Age-related declines in both epilepsy and controls
  - Epilepsy patients with accelerated thinning

Aging Effects in Epilepsy



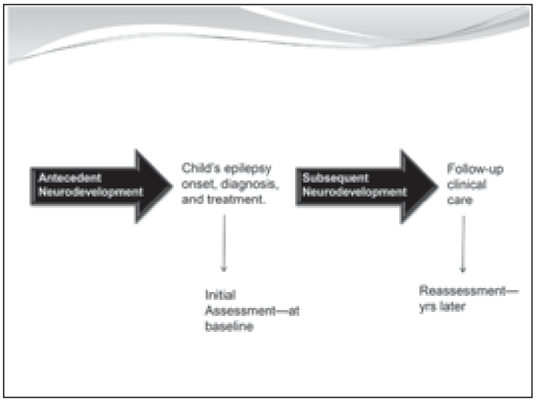
CRITICAL REVIEW AND INVITED COMMENTARY

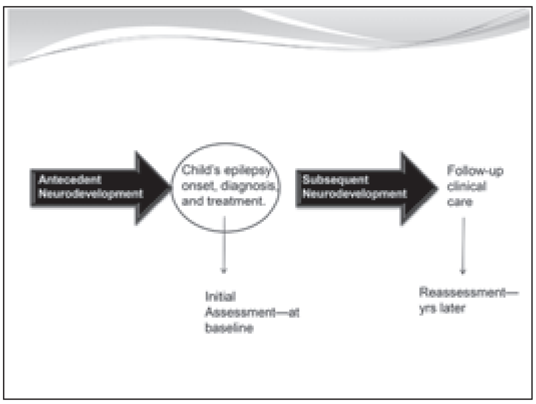
Growing old with epilepsy: The neglected issue of cognitive and brain health in aging and elder persons with chronic epilepsy

*†Bruce Hermann, ‡Michael Seidenberg, †‖Mark Sager, ‖¶Cynthia Carlsson, **Barry Gidal, *Raj Sheth, *†‖Paul Rutecki, and ‖¶Sanjay Asthana

*Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, U.S.A.; ‡Department of Psychology, Rosalind Franklin School of Medicine and Science, North Chicago, Illinois, U.S.A.; ‖Department of Medicine (Geriatrics), University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, U.S.A.; and ¶Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, U.S.A.; ¶GRECC, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, U.S.A.; **School of Pharmacy, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, U.S.A.; and ‖Department of Neurology, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, U.S.A.

Question 2—Neurodevelop


Antecedent Neurodevelopment
Child's epilepsy onset, diagnosis, and treatment.
Subsequent Neurodevelopment
Follow-up clinical care
Initial Assessment—at baseline
Reassessment—yrs later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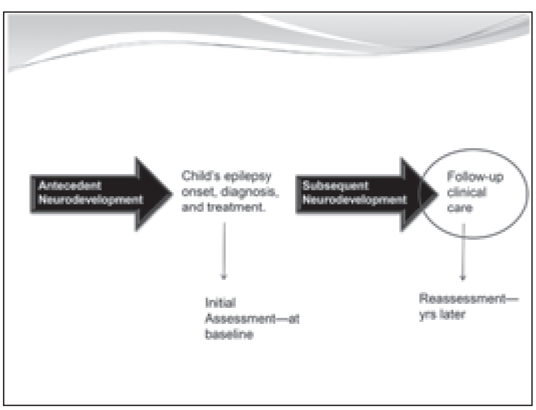
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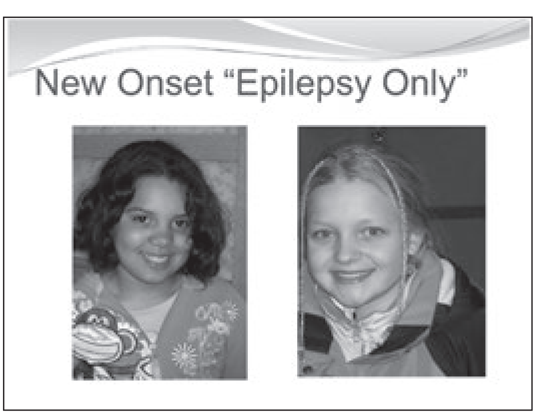
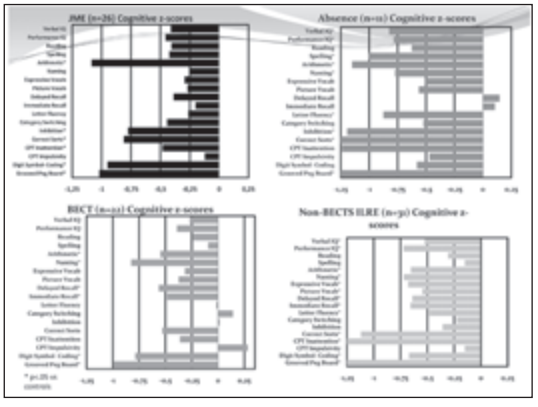

New Onset "Epilepsy Only"

Inclusion criteria

- Age 8-18
- Diagnosed within the past 12 months
- Normal neurological examination
- Normal clinical MRI
- No other developmental disabilities
- No other neurological disorder

Healthy controls—first degree cousins

Domain	Tests
Intelligence	WASI (Verbal IQ)
	WASI (Performance IQ)
Language	Boston Naming Test
	Expressive Vocabulary Test
	Peabody Picture Vocabulary Test-III
	D-KEFS (Letter Fluency)
Memory	CMS (Word Lists Learning)
	CMS (Word Lists Delayed)
Executive function	D-KEFS (Confirmed Correct Sorts)
	D-KEFS (Color-Word Interference Test: Inhibition)
	D-KEFS (Category Switching Accuracy)
	CCPT-II (Omission and Commission errors)
Motor function	Grooved Pegboard
	WISC-III (Digit Symbol-Coding)



Rates of DSM-IV Disorders in Children with Epilepsy versus Controls

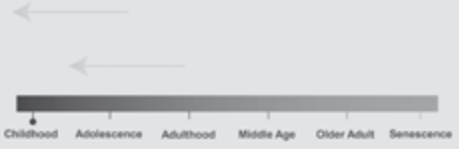
	Controls %	*Epilepsy* %
Depressive disorders	4.0	22.6
Anxiety disorders	22.0	35.8
Psychotic disorders	2.0	1.9
ADHD	10.0	26.4
Oppositional defiant disorders	2.0	13.2
Conduct	0.0	3.8
Tic disorders	2.0	9.4

*Totals will exceed 100% due to comorbid diagnoses.

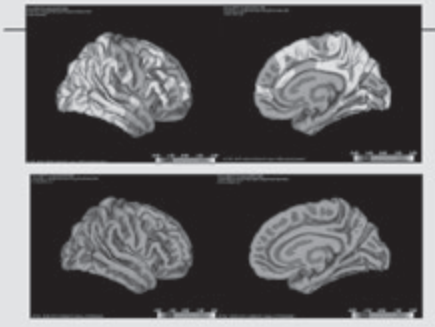
Prior to epilepsy onset

- **Cognitive/Academic Problems**
  - 26% received had academic problems at school prior to seizure onset (compared to 4% of controls)
- **Psychiatric Complications**
  - 45% experienced an Axis I disorder **prior** to first recognized seizure
  - 35.1% sought mental health assistance **prior** to seizure onset (counselor, psychiatrist, psychologist)

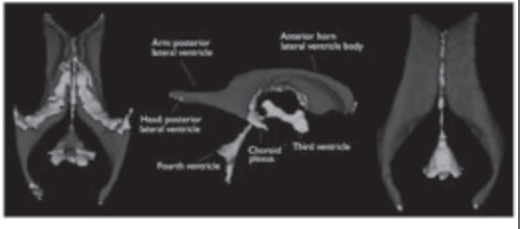
Neurodevelopment



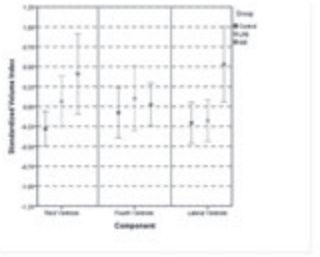
Childhood to Adolescence

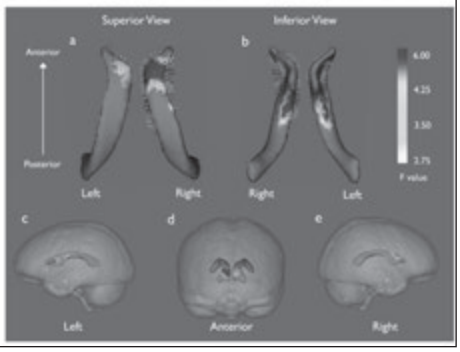


Ventricles



Ventricles

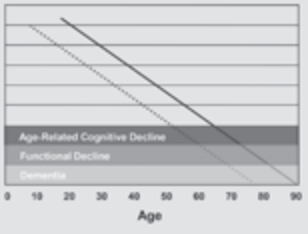




Summary of Life Span Effects

- Effects of disordered substrate
  - Neurobehavioral problems prior to and / or at seizure onset
- Subsequent neurodevelopmental effects
  - Effects of epilepsy and treatment on brain development
  - Effects of epilepsy and treatment on cognitive development
- Chronicity effects
  - Altered trajectory of cognitive change
  - Frank cognitive decline
- Accelerated aging effects
  - Active epilepsy
  - Remitted epilepsy

Life Span Threshold

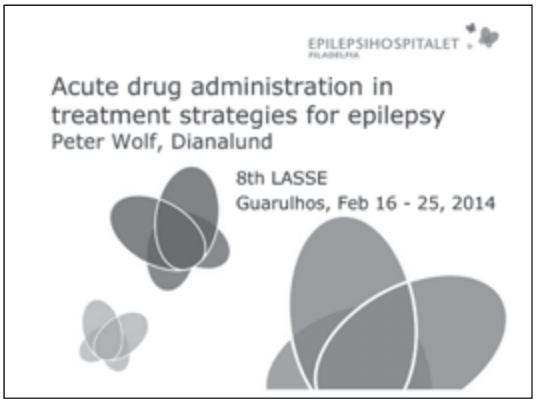


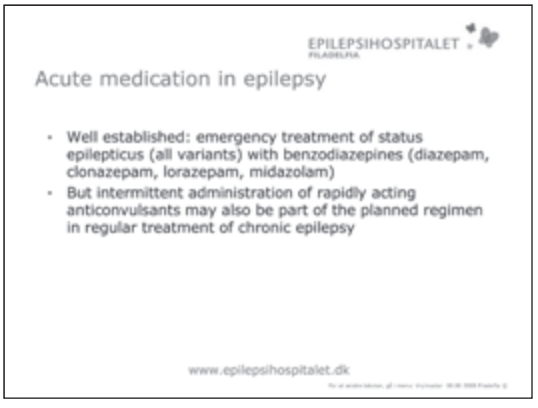
ANDRES KANNER (USA)

PSYCHIATRIC EFFECTS OF AEDS

Peter Wolf (Denmark)

ACUTE TREATMENT OF EPILEPSY





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Pat. Gitte O, age 26

- Family history: brother with CAE and GTC, controlled by VPA
- Own 1st GTCS age 26 on return from stay in USA
- Sleep deprived EEG: generalized SW and PSW
- In 3 years 6 GTCS always on awaking, always after party with much wine
- Declines AED treatment, want to use self-control
- At age 32 after more szs in identical situations treatment with LTG accepted
- At 300 mg still sz (with typical provocation)
- At 400 mg seizure free

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Pat. Gitte O, age 39

- After 3 years without seizures, start of slow stepwise dose reduction of LTG
- At 100 mg relapse of szs, still with identical triggers
- Does not want to increase dose again since no cure
- Detailed description of szs event:
  - Always in the morning after a party
  - First signs: is slightly confused, unconcentrated, can't remember what wants to do: ?
  - mild absence status
  - Tries to get back to sleep: if successful, nothing happens, otherwise GTCS after 10 min to later in the morningg

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Pat. Gitte O: only provoked szs, with well-defined prodrome

- The treatment of such patients can focus on the single seizure events to prevent them at perceived risk
- Here rapid action (< 10 min) is desired
- Choice of
  - Rectal Diazepam
  - Buccal Midazolam
  - Nasal Lorazepam

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Pat. Gitte O: only provoked szs, with well-defined prodrome

- The treatment of such patients can focus on the single seizure events to prevent them at perceived risk
- Here rapid action (< 10 min) is desired
- Choice of
  - Rectal Diazepam
  - Buccal Midazolam
  - Nasal Lorazepam
- Patient stops continuous LTG intake after 2 successful preventions
- Now seizure free since 4 years, uses ADA 3-5 / year, very happy with this solution

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Advantages for patient

1. No need for continuous drug intake
2. Improved therapeutic success
3. Establishment of self-control

Rationale: seizures are not unpredictable (or only sometimes)

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Aspect of self - control

- Numerous investigations of "locus of control" have demonstrated that many patients with epilepsy have externalised control perceptions
- Relate both to health and to life in general
- These seem to be related to the unpredictability of seizures that constitutes an important source of insecurity
- These patients do not believe that they have adequate control of their lives
- Self-perception of inferiority
- Re–establishment of internal control is highly important for patient's quality of life

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Target 1: the predictable seizure

- Literature example: catamenial epilepsy
- Feely & Gibson, *JNNP* 1984; 47: 1279-1282: administration of 20 - 30 mg Clobazam / day for 10 days around menstruation (to prevent development of BZD tolerance and minimize side effects).
- Best results if szs occur *only* with menstruation (rare). Some of these ptt got seizure free.
- Otherwise at best relative succes (improvement)
- More typically same amount of szs but at other times

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Interval treatment of catamenial epilepsy: almost forgotten

- The Feely & Gibson paper after 27 yrs is still hit nr. 20 in google for "catamenial epilepsy"
- Engel & Pedley 2nd ed 2008: not mentioned as treatment option
- Foldvary-Schaefer & Falcone, Neurology 2003; 61: S2 - S15: "cyclic use of BZDs or conventional AEDs proposed. ... Evidence for the effectiveness comes from small, unblinded series or anecdotal reports."

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Target 2: Lothar U., f.1953, left TLE with MTS

- Communal clerk, well married, two children, moves around on bicycle
- Onset in childhood, seizures never controlled
- Seizure type: cps with oral automatisms and speech arrest or aphasia
- Course from 1988-2003: almost no month without seizures, at best only 1-2/mth
- From 1993 increasing tendency for clusters of 3-4 seizures in 1-2 days. Stays at home after a seizure, loses workdays
- No interest in surgical treatment option

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Lothar U., f.1953, left TLE with MTS

- XII/95: 20 mg Clobazam (CLB) after 2. seizure
- VI/96: same dose after 1. seizure since limitation to 2 seizures makes no difference
- Hereafter 3 clusters of 2-3 seizures in 1997, 1998 and 2000
- Uses CLB 1 – 2 / mth
- In parallel consecutive administration of newer AEDs, no further improvement but
- whereas the seizure clusters caused a situation which he couldn't handle any more, his life has now returned to normal

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Target 2: clusters of seizures

- The most characteristic pattern of repetition in temporal lobe epilepsy: clusters at intervals
- Often therapy resistant
- If there is no surgical option the best compromise must be found between relative succes and burden of drugs
- ADA can make a big difference
- This is an aspect that has been totally neglected by therapy studies

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Prevention of clusters: literature

- Milligan et al. A clinical trial of single dose rectal and oral administration of diazepam for the prevention of serial seizures in adult epileptic patients.
  - *J Neurol Neurosurg Psychiat 1984; 47:235-240*
- One of few randomised controlled studies of ADA
- Provided proof of principle
- No study of practical usefulness available

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Acute drug administration (ADA)

Indications

1. Prevention of generalized tonic-clonic seizures (GTCS) after minor seizures (absence, myoclonic, simple focal or aura)
2. Prevention of seizures in patients with perceived risk of seizures or triggering factors.
3. Prevention of clusters of seizures
4. Prevention of status epilepticus (e.g. in febrile szs)

Choice of drug depends on available time

Usually oral Clobazam 10 – 20 mg

If rapid action desired: rectal diazepam, buccal midazolam, nasal lorazepam

Brand new: diazepam autoinjector

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To what extent is ADA used in epilepsy treatment?

- No systematic reports, but sometimes found as advice for example in patient information sheets or in the internet
- One frequent recommendation: preflight use of a BZD with long-distance flights (or other overnight travel)
- Increased risk because of sleep withdrawal, jet lag

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EPILEPSIHOSPITALET FILADELFIA

ADA: 24 own patients with uncontrolled szs

Indications for ADA

- Intervention at prodrome / aura: 8
- Seizure prevention at perceived risk: 8
- Prevention of clusters: 8

Note: all patients are adults. In a pediatric centre febrile seizures would be an important indication

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EPILEPSIHOSPITALET FILADELFIA

ADA: 24 own patients with uncontrolled szs

- Free of all szs 5
- Free of disabling szs 1 } 44%
- > 50% reduction 4
- Minor reduction / no change 11
- Undetermined 3

- Compliance:
  - Always correct use of ADA 10
  - Mostly correct use 7
  - Sporadic / not used at all 7

Patient satisfaction very high (63/88%) because they are given a means of efficient self-control

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EPILEPSIHOSPITALET FILADELFIA

Why is compliance a problem with ADA?

- Decision to apply
  - Recognition of indication
    - Subjective
    - Objective
    - Cooperation of caretaker may be required
  - Narrowing of consciousness during pathological state
- Learning phase
  - Experience of success
  - Some pats never try because sceptical
- Availability

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EPILEPSIHOSPITALET FILADELFIA

Wolf P: Acute administration of benzodiazepines as part of treatment strategies for epilepsy. CNS Neuroscience & Therapeutics 2010 (online)

"Conclusions: ADA is an elegant and often successful but underused treatment option for selected patient groups where it can make the difference between becoming seizure free or not. Depending on the individual case it can be applied as monotherapy or in combination with a basis AED."

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ADA: add-on versus monotherapy

- Add-on to continuous AED treatment: 22
- ADA as monotherapy: 2
- Secondary conversion to monotherapy after proof of effect: 3

Thus now on ADA as monotherapy: 5 pat (20%)

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Conclusion

EPILEPSIHOSPITALET FILADELFIA

- Beyond traditional emergency treatment of status epilepticus, acute ad hoc medication can be used to
  - prevent clusters of seizures (after first szs.)
  - prevent full-blown seizures (GTC, CP) by intervention at aura/prodrome
  - prevent seizures in situations of known increased risk or social occasions (theatre etc.)
  - As add-on in episodes with increased seizures
- Acute medication can supplement continuous conventional AED treatment or stand alone

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EPILEPSIHOSPITALET
FILADELFIA

Wolf P. Acute drug administration in epilepsy: A review. CNS Neuroscience & Therapeutics 2010 (online)

Reviewed indications:

- Febrile convulsions (well established)
- Non-febrile prolonged seizures in children (like FC)
- Clusters of seizures (proof of principle in controlled study)
- Catamenial seizures (weak evidence)
- Response to "warnings"
- Reflex epilepsy (good evidence in hot water epilepsy)
- Lifestyle-provoked seizures
- Social situations and travel
- Prevention of withdrawal seizures

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EPILEPSIHOSPITALET
FILADELFIA

Wolf P. Acute drug administration in epilepsy: A review. CNS Neuroscience & Therapeutics 2010 (online)

Reviewed drugs

- Diazepam
- Midazolam
- Lorazepam
- Other benzodiazepines
- Acetazolamide (catamenial szs)
- Chloral hydrate
- Valproic acid suppositories
- Pyridoxine in febrile convulsions (conflicting reports)
- Antipyretics in febrile convulsions (no effect)

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EPILEPSIHOSPITALET
FILADELFIA

Wolf P. Acute drug administration in epilepsy: A review. CNS Neuroscience & Therapeutics 2010 (online)

"The drugs most commonly used for ADA are the benzodiazepines diazepam (oral or rectal), clobazam and buccal or nasal midazolam and lorazepam. …

The best evidence for the efficacy of ADA exists in febrile and nonfebrile childhood seizures, whereas the evidence in catamenial epilepsy is weak. Prevention of clusters is a well-proven principle but its application has been little studied. Prevention of imminent seizures predicted by well-established triggers, defined risk factors, or premonitory minor seizure activity seems to be at the same time the most intelligent and the least investigated application of ADA and would deserve to be better studied."

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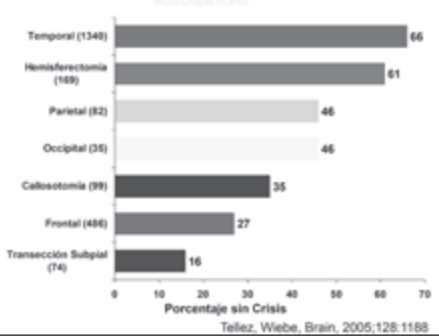
Lilia Morales Chacon (Cuba)

TRANSCRANIAL MAGNETIC STIMULATION IN EPILEPSY REFRACTORY TO DRUG TREATMENT

Estimulación magnética transcraneal en las epilepsias

Lilia M. Morales Chacón. MD, PhD.
La Habana, Cuba.

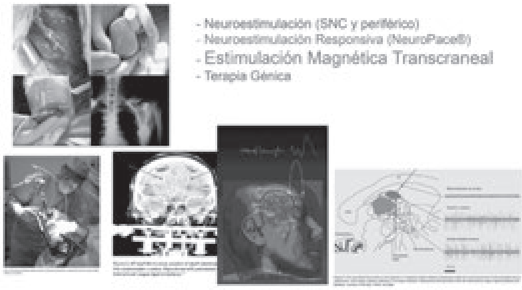
La terapia quirúrgica es más eficiente que la farmacoterapia y resulta la única modalidad de tratamiento curativa en las epilepsias intratables con medicamentos.



Tellez, Wiebe, Brain, 2005;128:1188

TERAPIAS NEUROMODULADORAS

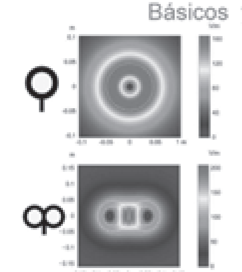
- Neuroestimulación (SNC y periférico)
- Neuroestimulación Responsiva (NeuroPace®)
- Estimulación Magnética Transcraneal
- Terapia Génica



	Disease (Clinical Evaluation FDA Status)	Waveform control	Targeting Ability	Invasiveness / Side effects	Application Environment	Selected Companies
Electroconvulsive Therapy (ECT)	Depression[4], Mania[4]	Poor - Pulse train only	Poor Non-focal	Non-invasive / Brain Damage, memory loss	Requires trained clinical staff	Somatics, MECTA, Ectron, Elcot, Medcraft
Vagus Nerve Stimulation (VNS)	Epilepsy[4], Depression (debated)[4]	Poor - Pulse train only with indirect modulation	Indirect Unknown	Invasive, implanted pacemaker and electrodes attached to vagus nerve	Requires trained clinical staff for deployment and optimization	Cyberonics
Deep Brain Stimulation (DBS)	Parkinson[4], Epilepsy[3], Depression[3], Dystonia[4]	Moderate - brief balanced pulses	Excellent	Invasive. Perforation of skull and implanted pacemaker electrodes	Requires trained clinical staff for deployment and optimization	Medtronic, St Jude (ANS)
Transcranial Magnetic Stimulation (TMS)	Depression[4], Bipolar[2], OCD[2], Post-Traumatic Stress[2], Schizophrenia[2] Stroke Rehabilitation[2]	Poor – Brief pulse trains, seizure risk	Good	Non-invasive. External Magnetic Field / Seizures., Acute Pain, Potential memory loss	Requires trained clinician, hospital setting (seizure risk)	Magstim, Schwarzer GmbH, Medtronic, Dantec Dynamics, Neuronetics, Mouba.Mag-Venture, Nexstim, Neuralieve, Brainsway
Transcranial Direct Current Stimulation (tDCS)	Stroke Rehabilitation[2], Depression[2], Dystonia[2], Improvement in: Memory[2], Learning[2], amblyopic eye[2]	Poor – DC current	Poor	Non-invasive, DC current between two scalp electrodes / Bi-phasic effects	Robust/simple, potential for home use	Neuroconn, Magstim
High-Density Transcranial Electrical Stimulation (HD-tES)	Customizable*	Excellent	Good / Excellent	Non-invasive, arbitrary waveform between two+ scalp electrodes	Robust/simple (computer guided), Potential for home use	

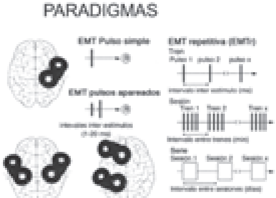
1= Clinical Trial Phase I
2=Clinical Trial Phase II
3=Clinical Trial Phase III
4=Clinical Trial Phase IV
A=FDA Approved
U= Under Clinical Trial

Estimulación Magnética Transcraneal. Principios Básicos y Protocolos



El campo eléctrico generado, la focalidad y penetración del estimulo, dependen de la geometría de la bobina.

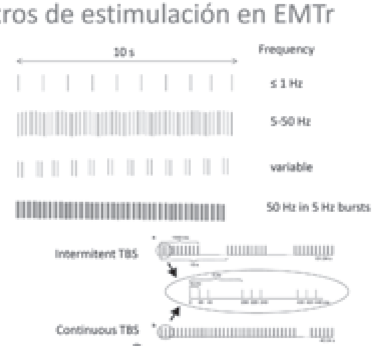
PARADIGMAS



Representación esquemática de las diferentes formas de aplicar estimulación magnética transcraneal: pulsos simples, pulsos apareados en una o dos áreas diferentes del cerebro y estimulación magnética transcraneal repetitiva (lenta o rápida)

Parámetros de estimulación en EMTr

- Low frequency
- High frequency
- Paired stimulation
- Theta bursts stimulation(TBS)



Cuál resulta el mejor en función de la patología?

Protocolos EMTr (online vs offline)

Diferentes aplicaciones en la clínica y en la investigación

Efecto de la EMTr:

- Disruptivo (local)

Durante la estimulación se puede interferir con los procesos cerebrales que se están desarrollando en ese instante

- Terapéutico (local y distante)

La estimulación provoca cambios en la eficacia de la transmisión sináptica en las redes neuronales sobre las que actúa; esto tiene una expresión funcional que se puede comprobar desde el cese de la estimulación, y cuya duración dependerá del reforzamiento de la propia estimulación

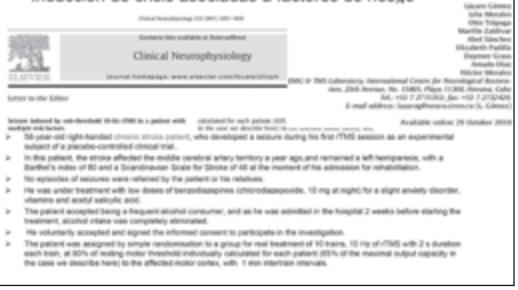
Seguridad y Tolerabilidad de la EMTr

Efectos adversos

Efecto adverso	rTMS
Convulsión	Reportado, infrecuente
Cefalea	Frecuente
Escozor	No
Ardentía	No
Mareos	Sí
Cervicalgia	Frecuente
Postdescargas, difusión de la excitabilidad	Reportado, infrecuente
Trastorno de memoria	No

Seguridad y Tolerabilidad de la EMTr

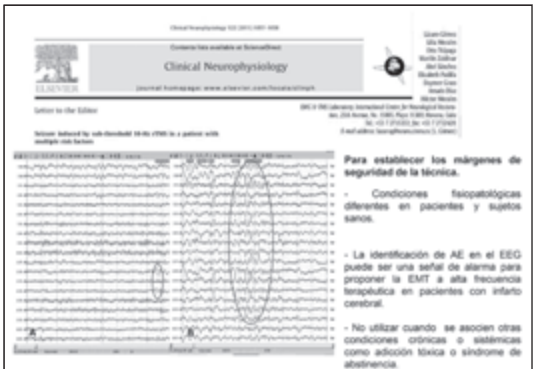
Inducción de crisis asociadas a factores de riesgo



Clinical Neurophysiology

Letter to the Editor

- 58-year-old right-handed chronic stroke patient, who developed a seizure during his first rTMS session as an experimental subject of a placebo-controlled clinical trial.
- In this patient, the stroke affected the middle cerebral artery territory a year ago,and remained a left hemiparesis, with a Barthel's index of 80 and a Scandinavian Scale for Stroke of 48 at the moment of his admission for rehabilitation.
- No episodes of seizures were referred by the patient or his relatives.
- He was under treatment with low doses of benzodiazepines (chlorodiazepoxide, 10 mg at night) for a slight anxiety disorder, vitamins and acetyl salicylic acid.
- The patient accepted being a frequent alcohol consumer, and as he was admitted in the hospital 2 weeks before starting the treatment, alcohol intake was completely eliminated.
- He voluntarily accepted and signed the informed consent to participate in the investigation.
- The patient was assigned by simple randomisation to a group for real treatment of 10 trains, 10 Hz of rTMS with 2 s duration each train, at 90% of resting motor threshold individually calculated for each patient (65% of the maximal output capacity in the case we describe here) to the affected motor cortex, with 1 min intertrain intervals.



Clinical Neurophysiology

Letter to the Editor

Para establecer los márgenes de seguridad de la técnica.

- Condiciones fisiopatológicas diferentes en pacientes y sujetos sanos.

- La identificación de AE en el EEG puede ser una señal de alarma para proponer la EMT a alta frecuencia terapéutica en pacientes con infarto cerebral.

- No utilizar cuando se asocien otras condiciones crónicas o sistémicas como adicción tóxica o síndrome de abstinencia.

Psychiatry Research

Review article

rTMS for adolescents: Safety and efficacy considerations

Douglas D'Agati[a], Yuval Bloch[b], Yechiel Levkovitz[b], Irving Reti[a,c]*

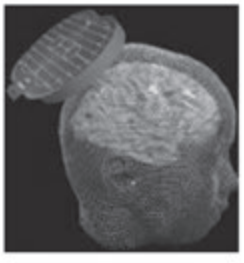
Recommandations françaises sur l'utilisation de la stimulation magnétique transcrânienne répétitive (rTMS) : règles de sécurité et indications thérapeutiques[☆]

French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): Safety and therapeutic indications

Seguridad Y Tolerabilidad de la EMTr

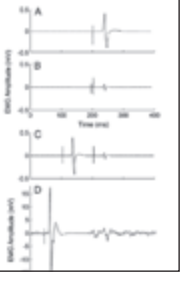
- Incidencia de crisis en una sesión de EMTr: pacientes con epilepsia > sujetos no epilépticos.
- Parámetros del estimulo que aumentan la probabilidad de efectos adversos.
- EMTr a alta frecuencia induce crisis atípicas (originadas en el sitio de estimulación más que en la ZE) Duhuna 1991. La EMT a baja frecuencia induce crisis habituales (Theodore 2002, Bae 2007).
- En general, el riesgo reportado es bajo aunque se precisan más estudios.

Estimulación Magnética Transcraneal Investigación y Diagnóstico.

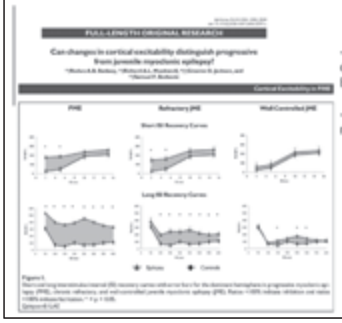


Parámetros EMT- EMG utilizados para la Investigación y el diagnóstico

MEDICIONES CON EMT DE LA CORTEZA MOTORA EVALUAN ASPECTOS DE LA EXCITABILIDAD CORTICAL



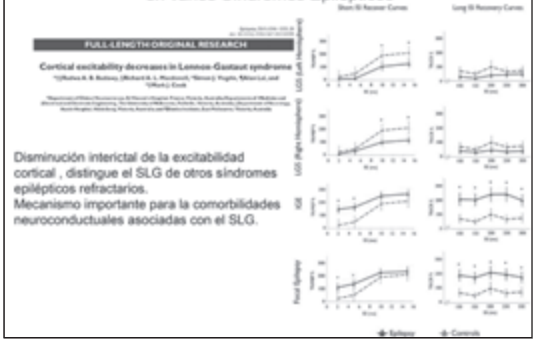
EMT en la evaluación de la Excitabilidad Cortical en varios Síndromes Epilépticos



- Aumento de la excitabilidad cortical en los pacientes con Epilepsia Mioclónica Progresiva

- No diferencias en el umbral motor entre EMJ y EMP

18.4.1 EMT en la evaluacion de la excitabilidad cortical en varios Síndromes Epilépticos



Disminución interictal de la excitabilidad cortical , distingue el SLG de otros síndromes epilépticos refractarios.
Mecanismo importante para la comorbilidades neuroconductuales asociadas con el SLG.

EMT en la evaluación de los cambios en la excitabilidad cortical en la transición entre estados interictal e ictal.

TMS studies of preictal cortical excitability change

Las respuestas motoras a la EMT difieren en los estados:

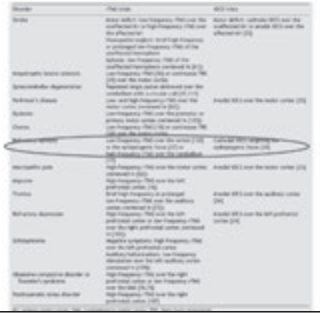
- Interictal
- Preictal (aumento de la excitabilidad o disminucion de la inhibicion)
- Postictal

EMT en el Mapeo Funcional de Áreas Corticales elocuentes y en la localización pre-quirúrgica de la ZE.

Non-invasive preoperative localization of primary motor cortex in epilepsy surgery by navigated transcranial magnetic stimulation

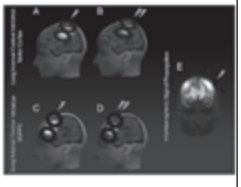
Estimulación Magnética Transcraneal Terapéutica

APLICACIONES TERAPÉUTICAS DE LA EMT PROTOCOLOS UTILIZADOS



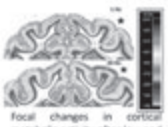
Razones del uso de la EMT en la terapéutica

- ✓ La EMTr produce un efecto que dura minutos u horas después de la aplicación del estímulo.
- ✓ Modula la actividad neuronal en el área blanco de la corteza disfuncional provocando beneficio funcional.
- ✓ La naturaleza del efecto depende de la frecuencia, intensidad y tiempo. La EMTr a alta frecuencia (>5 Hz) aumenta la excitabilidad cortical especialmente si se utilizan intensidades altas (efecto proconvulsivante). Ziemann U, 2005
- ✓ La EMTr a baja frecuencia (0,2-1 Hz) reduce la excitabilidad cortical lo que se demuestra con el incremento en la duración del periodo silente cortical (Cincotta M 2003) y con la reducción de la amplitud del potencial evocado motor (Muellbacher W 2000).

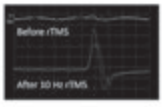


Mecanismos /efectos de la EMTr

Local effects

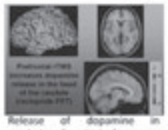


Focal changes in cortical metabolic activity after low and high rTMS

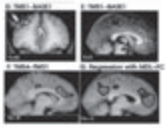


LTP like effect on MEP

Distant effects(brain conectivity)



Release of dopamine in caudado after high frequency rTMS of L DLPFC



Razones del uso de la EMT en la terapéutica

- ✓ Estos efectos son reminiscencias de la potenciación y la depresión a largo plazo dos formas de plasticidad sináptica provocadas en los circuitos corticales en modelos animales por estimulación eléctrica a alta – baja frecuencia respectivamente
- ✓ Contribución de los astrocitos y gliotransmisores los fenómenos de LTP Y LTD.
- ✓ Efecto de la EMT a baja frecuencia en la expresión del NPY y en la apoptosis de neuronas hipocampales de ratas epilépticas inducidas por pilocarpina

Frontiers in
COMPUTATIONAL NEUROSCIENCE

REVIEW ARTICLE

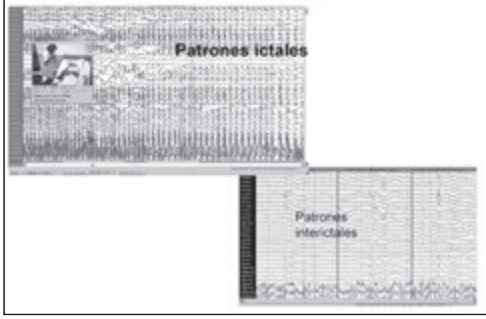
Astroglial networks and implications for therapeutic neuromodulation of epilepsy

*Mark R. Witcher * and Thomas L. Ellis*

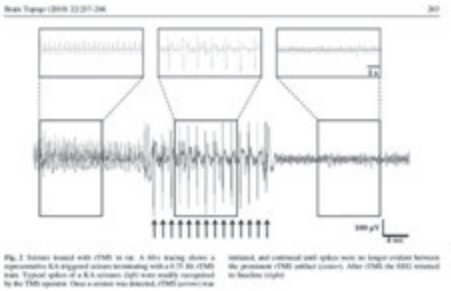
Fármacos que modifican el efecto de la rTMS/TDCS

Medicamento	TMS		TDCS	
	Excitabilidad	Inhibición	Estimulación anodal	Estimulación catódica
Gabapentin		▲		
Benzodiazepinas (lorazepam)	▼	▲	▼ ▲	
Carbamazepina Oxcarbamazepina	▼		▼	
Valproato				
L-dopa	▼	▲	▼	▲
AD Triciclicos				
Fluoxetina	▲		▼	
Dextrometorfan			▼	▼
Antiparkinsonianos	▲	▼	▲	
propanolol			▼	
Haloperidol	▼		▲	
Pentotal	▼			
Lamotrigina		▲		
Progesterona		▲		

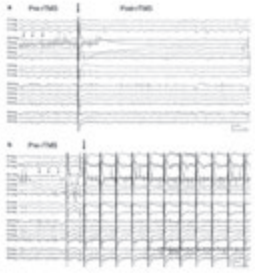
Ensayos Clínicos.....
ESTADOS INTERICTAL/ICTAL



Se puede detener una crisis epiléptica?



Ensayos Clínicos…..
EMTr /estado ictal/EPC

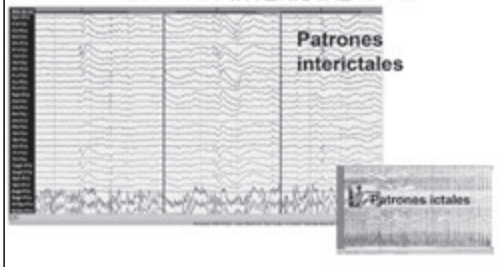


EMTr en Epilepsia parcial continua

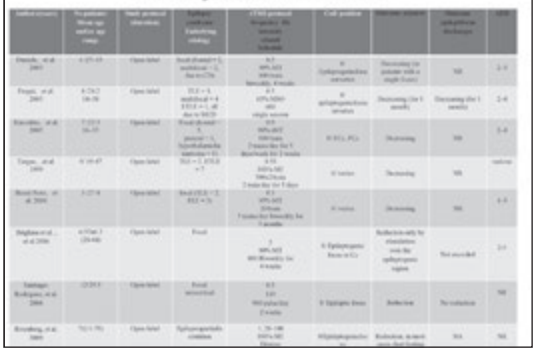
Table 2
Summary of published cases of EPC treated with rTMS

Patient	Age	Etiology	Coil position	rTMS intensity	rTMS frequency	Train duration	Number of trains	Outcome	Adverse events
1 [8]	7	Unknown, focal cortical atrophy on MRI	Seizure focus	90% MO	20 Hz	2 s	15	Clinical seizure became intermittent and stopped in 2/15	None reported
2 [8]	11	Unknown, focal cortical atrophy on MRI	Seizure focus	110% MT	20 Hz	2 s	15	No change in clinical seizure, improved EEG	None reported
3 [11]	40	Unknown Normal MRI	Seizure focus	100% MT	0.5 Hz	300 s	10 (1 train/session, biweekly, for 4 weeks)	Clinical seizure decreased during rTMS, and decreased further on follow-up	None reported
4 [9]	31	Cortical dysplasia	Seizure focus	90% MT	0.9 Hz	108 s	1	Clinical seizure stopped, resumed in 2 months, and stopped again with rTMS	None reported
5 [10]	8	Neuronal ceroid lipofuscinosis (probable)	Seizure focus	100% MO	0 Hz (train 5 Hz)	0 Hz: 5 s 1 Hz: 600 s	2/3 Hz, one preceded by five trains at 0 Hz	No change	None reported
6 [10]	16	Perinatal stroke	Seizure focus	765 MO	0 Hz, (train 1 Hz)	0 Hz: 5 s 1 Hz: 900 s	2/3 Hz, one preceded by 4 trains at 0 Hz	No change	Mild headache and leg pain

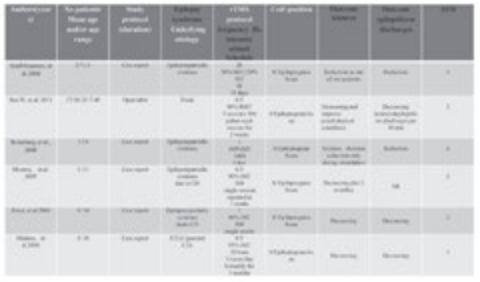
Ensayos Clínicos…..
ESTADOS INTERICTAL/ICTAL



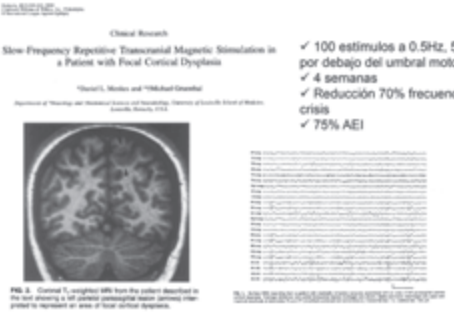
Ensayos Clínicos…..



Ensayos Clínicos…….



Ensayos Clínicos

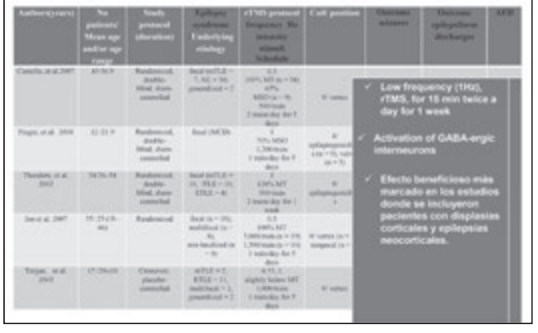


Clinical Research

Slow-Frequency Repetitive Transcranial Magnetic Stimulation in a Patient with Focal Cortical Dysplasia

- ✓ 100 estímulos a 0.5Hz, 5% por debajo del umbral motor
- ✓ 4 semanas
- ✓ Reducción 70% frecuencia de crisis
- ✓ 75% AEI

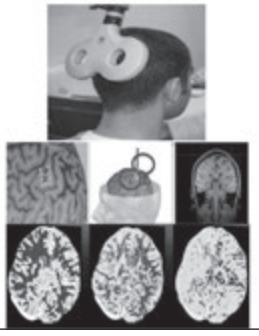
Ensayos Clínicos



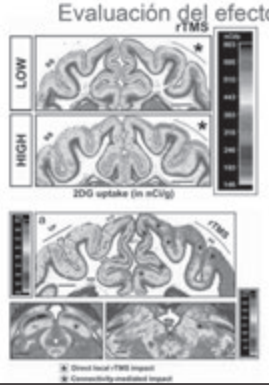
- ✓ Low frequency (1Hz), rTMS, for 15 min twice a day for 1 week
- ✓ Activation of GABA-ergic interneurons
- ✓ Efecto beneficioso más marcado en los estudios donde se incluyeron pacientes con displasias corticales y epilepsias neocorticales.

Evaluación del efecto de la EMT

- Evolución clínica.
- Electrofisiología.
- Neuroimagenes



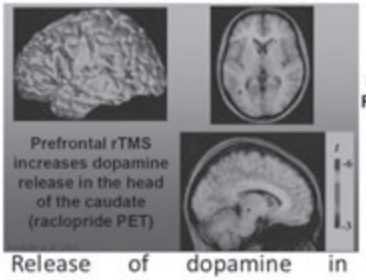
Evaluación del efecto de la EMT



NEUROIMAGENES FUNCIONALES

Impacto de la estimulación magnética transcraneal sobre el metabolismo cerebral demostrado por la alteración en la captación de 2-deoxiglucosa (2-DG) en el gato.

Evaluación del efecto de la EMT

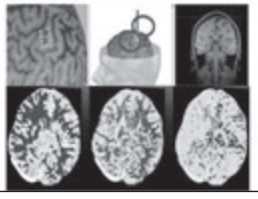


NEUROIMAGENES FUNCIONALES

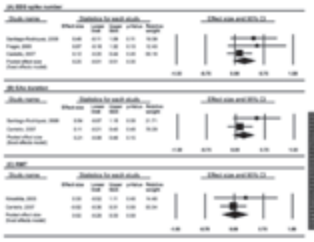
Release of dopamine in caudado after high frequency rTMS of L DLPFC

Evaluación del efecto de la EMT

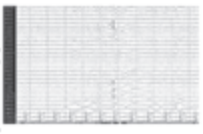
- Evolución clínica.
- Electrofisiología.
- Neuroimagenes.



Evaluación del efecto de la EMT
ELECTROFISIOLOGIA

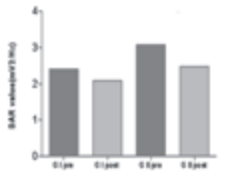


Datos disponibles limitados sobre el efecto de la EMT en las características del EEG y en el umbral motor de reposo.

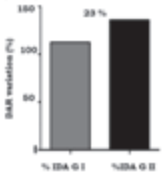


Statistical summary and forest plot for fixed effects meta-analysis of effect size for (A) EEG spike number, (B) EAs duration and (C) RMT.

Modificaciones del EEG cuantitativo en pacientes sometidos a EMTr a baja frecuencia vs grupo control



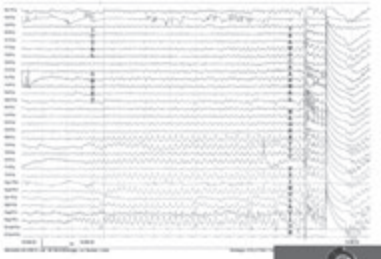
Global Delta/alpha ratio (mV2/Hz) obtained from EEG recording before and after rTMS sessions in stroke patients submitted to sham rTMS (GI) and those submitted to real 1Hz-rTMS (GII).



Delta/alpha ratio variation per group. Note the Delta/alpha ratio (DAR) parameter highly decreased in GII after 1Hz-rTMs sessions.

Evaluación del efecto de la EMT

COREGISTRO EMT- EEG

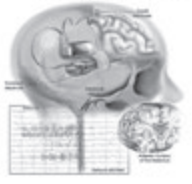


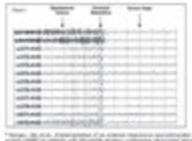
Monitoreo en tiempo real de la AE interictal e ictal durante la EMTr

Evaluación con fines diagnósticos de la excitabilidad cortical

Evaluación del efecto de la EMT

APLICACIONES DEL COREGISTRO EMT- EEG





- ✓ Diseño de protocolos terapéuticos de EMTr
- ✓ Probar algoritmos para detección de crisis epilépticas en combinación con patrones de estimulación abortivos

CONCLUSIONES

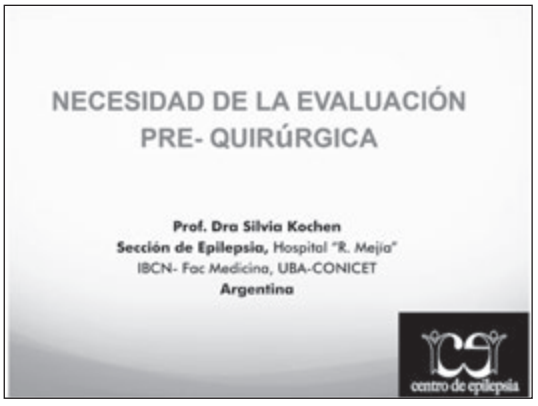
1. La EMTr debe considerarse a futuro como un método terapéutico no invasivo relativamente seguro y económico en pacientes con epilepsias medicamente intratables.
2. Se demostrado en los últimos años que la EMTr a baja frecuencia puede reducir la frecuencia de crisis y las descargas epileptiformes principalmente en aquellos pacientes con zonas epileptogénicas localizadas en la corteza como las MDC.
3. La eficacia antiepiléptica de la EMTr debe determinarse en ensayos clínicos randomizados y controlados que permitan evaluar el efecto placebo, esclarecer aspectos metodológicos de la técnica, criterios de inclusión de los pacientes, efectos de la MAE así como las medidas de evolución

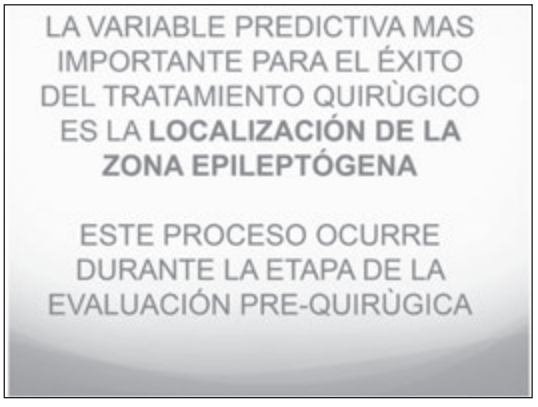
FUTURO

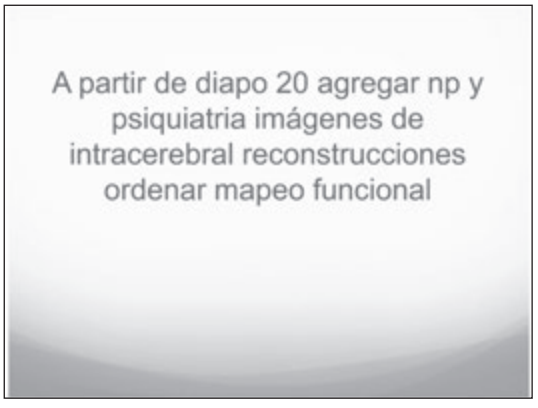
1. Determinar el efecto de la EMTr sobre la actividad eléctrica cerebral y otros estudios neurofuncionales que contribuyan a la comprensión de los mecanismos funcionales que median en el efecto de la EMTr en las epilepsias.
2. Desarrollo de las aplicaciones del coregistro EMTr-EEG
3. Información sobre los riesgos potenciales de la EMTr en la inducción de crisis en pacientes con epilepsia.
4. Establecer parámetros de estimulación y criterios óptimos de selección de pacientes.

Silvia Kochen (Argentina)

THE NEED FOR PRESURGICAL EVALUATION







- Los pacientes con epilepsia resistentes, son los mayores consumidores de AEDs, y necesitan además otros cuidados médicos.
- Si la cirugía logra eliminar la incapacidad que le provocan las crisis:
  - tiene un gran impacto en el costo directo e indirecto provocado por la epilepsia
  - La reintegración en la sociedad del paciente, también justifica los costos que significan la cirugía de la epilepsia.

Cirugía de la Epilepsia – Candidatos

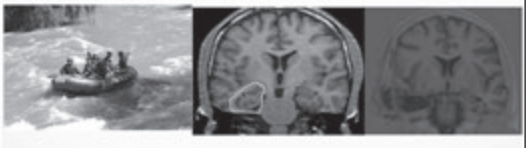
Epilepsia Parcial resistente a las AEDs

- Epidemiología:

- Prevalencia de epilepsia = 0.5-1% de población general
  60-70 % epilepsia parcial
  20-35% fármaco resistente

- Candidatos Potenciales a cirugía de la epilepsia
  = 0.03% de la población general

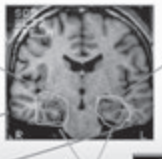
"Candidatos fáciles"

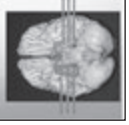


Nivel I: Epilepsia Temporales o Extratemporales lesiónales que no necesitan registros EEG invasivo (SEEG)

"Candidatos difíciles"

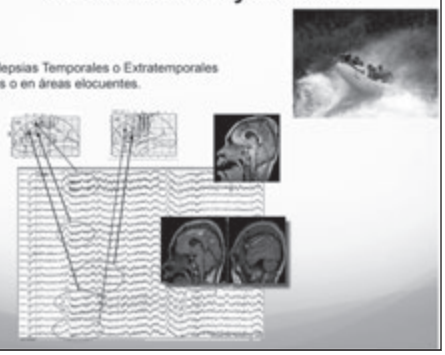
Nivel II: Epilepsia Temporales o Extratemporales lesiónales que necesitan SEEG.





"Candidatos muy difíciles"

Nivel III: Epilepsias Temporales o Extratemporales no lesiónales o en áreas elocuentes.



¿Cuánto tiempo debemos esperar para evaluar la posibilidad de cirugía ?

- **Epilepsia con severas y frecuentes crisis asociada con mala respuesta a las DAEs y retraso de pautas madurativas. En general se desencadenan durante el primer año de vida. Tiempo a esperar sugieren 3 meses (dos años es inaceptable).**
- **La mayoría de los centros considera dos intentos de monoterapia con y sin prueba de politerapia por un periodo en general de 2 años.**

Cirugía de la Epilepsia – Algoritmo

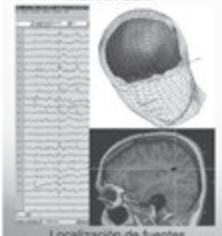
→ Metodos y Objetivos

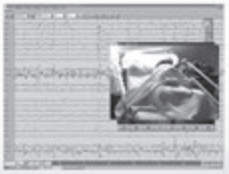
ZONA EPILEPTÓGENA?

Fase I Investigaciones
Electrofisiológicas no-invasivas

Video-EEG ictal + observación

Interictal EEG

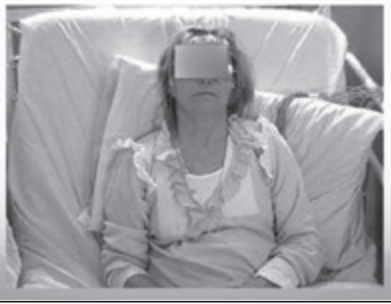




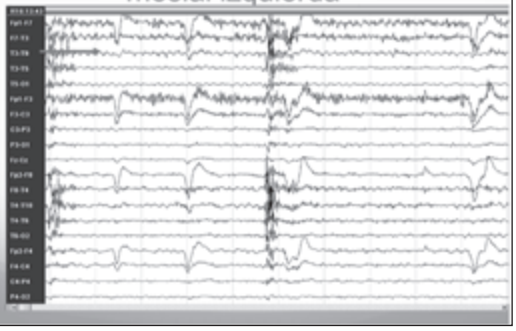
Localización de fuentes
de actividad paroxística

Correlación Electro - Clínica

Semiología: inicia con sensación de "sentirse perdida", "malestar epigástrico", luego ruptura de contacto e inmovilidad



Crisis de inicio en la región temporal mesial izquierda



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(81 pac.)

Giagante et al.

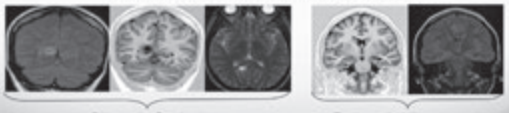
Cirugía de la Epilepsia – Evaluación Pre-quirúrgica Fase I investigación no-invasiva

Neuroimagen

MRI

→ Recomendaciones de la Comisión de ILAE

Determinación de lesión epileptogénica

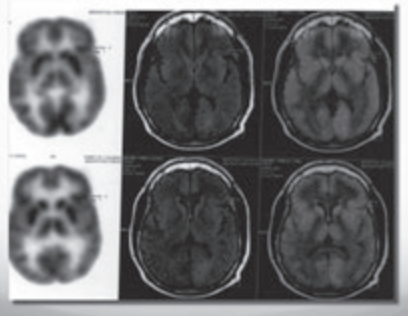


Displasia Cortical

Esclerosis Hipocampal

PET

- ELT: Hipometabolismo extenso 60-90%.
  - LF 30%
  - GB 45%
- EXTL: Hipometabolismo extenso 60%.
  - En ocasiones discreto, multilobar o difuso.
- Utilidad: IRM negativa
  - Datos no congruentes.
  - Planificación de EEG invasivo



EVALUACIÓN NEUROPSICOLÓGICA DEL PACIENTE CON EPILEPSIA
Candidato a Cirugía

Protocolo de Evaluación Neuropsicológico

- Valoración global del rendimiento del paciente y en función del resultado y del tipo de cirugía a realizar, se exploran las funciones mas relevantes
- Utilización del Protocolo de Evaluación Neuropsicológico

Neuropsicológico

- Inteligencia
- Dominancia Manual
- Memoria
- Lenguaje
- Atención
- Función Ejecutiva
- Calidad de Vida

Memoria Material Específico

Protocolo Evaluación NPS

- **Inteligencia:**
  Test de Inteligencia para Adultos (WAIS-III).
- **Dominancia manual**
  Cuestionario de Dominancia Manual de Edimburgo.
  Grooved Pegboard
- **Atención**
  Trial making test B (TMT B)
  Dígitos
  Test de cancelación de dígitos
  Modalidad Digito Simbolo

- **Memoria Visual (no verbal)**
  List Learning test (diseños)
  Test de la Figura Compleja de Rey

- **Memoria verbal**

List Learning test

(palabras)

Rey Auditory Verbal Learning Test (RAVLT)

Protocolo de Evaluación NPS

- **Escala Wechsler de Memoria** (WMS III)
  - **Modalidad mnésica**
- **Función ejecutiva**

Wisconsin Card Sorting Test (WCST)
Stroop test
Torre de Hanoi
Fluencia verbal fonológica

Protocolo de Evaluación NPS

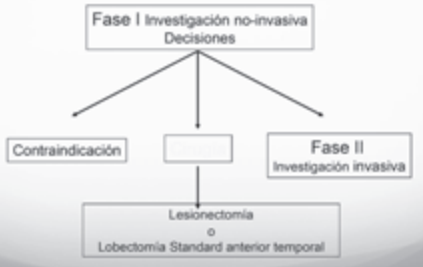
- **Lenguaje**

Test de denominación por confrontación visual de Boston
Token Test
Vocabulario, Comprensión, Analogías(sub escalas WAIS III)

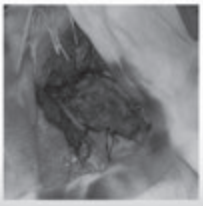
Protocolo de Evaluación Psiquiátrica

- La realización de entrevistas psiquiátricas con el paciente y los familiares L
- La confección de una historia clínica psiquiátrica
- La administración de entrevistas estructuradas del DSM IV (SCID I y II).
- En los pacientes operados se pautó un seguimiento periódico cada tres meses el primer año y cada seis meses el segundo y se readministró la SCID I.

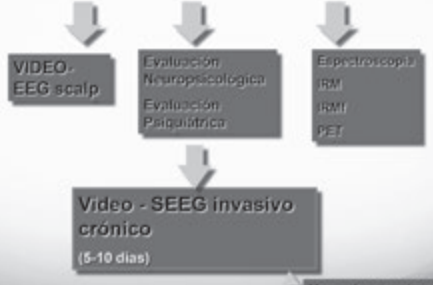
Cirugía de la Epilepsia – Evaluación Pre-quirúrgica



Lobectomía temporal izquierda



Si no se logra definir la Zona Epileptógena con:



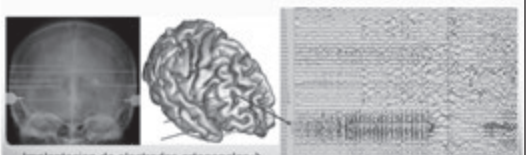
Principales indicaciones de Electrofisiología Invasiva

- Epilepsia temporal con crisis de inicio independiente
- Falta de congruencia entre IRM, V-EEG y estudios funcionales
- Zona epileptógena cercana o en areas elocuentes
- Revaloración de fallos quirúrgicos
- Epilepsia no lesional
- Imágenes estructurales no localizadas
- Patología dual
- Lesiones que se extienden fuera de las resecciones estándar
- Lesiones múltiples
- Síndromes electro clínicos atípicos

Cirugía de la Epilepsia – Evaluación Pre-quirúrgica

Fase II Investigación invasiva
Exploración Intracerebral

→ Estereo-electroencefalografia (SEEG)



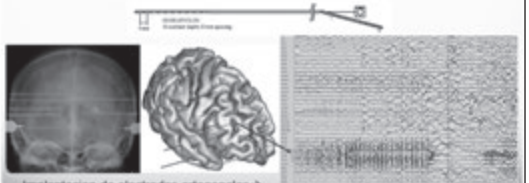
Implantacion de electrodos ortogonales→
64 canales de registro

Video-SEEG registro de actividad interictal,
Crisis y estimulación

Cirugía de la Epilepsia – Evaluación Pre-quirúrgica

Fase II Investigación invasiva
Exploración Intracerebral

→ Estereo-electroencefalografia (SEEG)



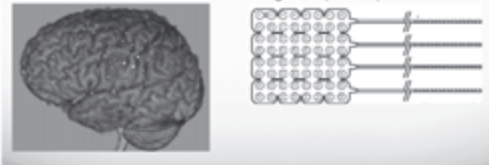
Implantacion de electrodos ortogonales→
64 canales de registro

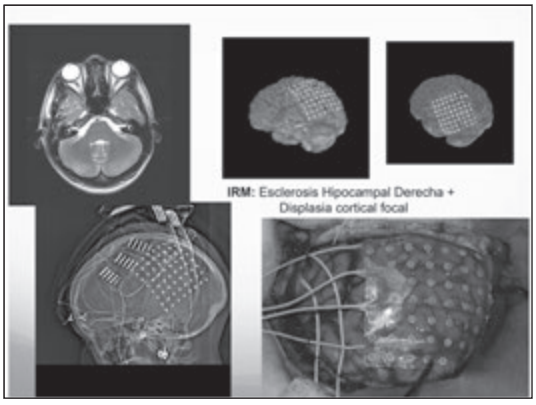
Video-SEEG registro de actividad interictal,
Crisis y estimulación

Cirugía de la Epilepsia – Evaluación Pre-quirúrgica

Fase II investigación invasiva
Exploración Intracerebral

→ Electrocorticografia (ECoG)



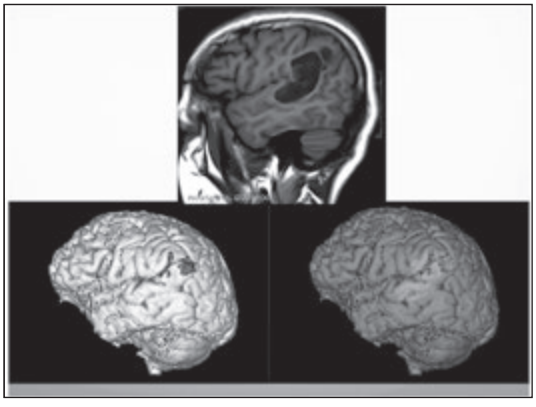


IRM: Esclerosis Hipocampal Derecha +
Displasia cortical focal

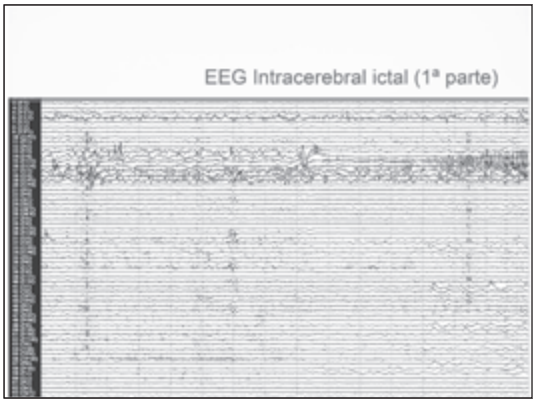
Evaluación Neurofisológica Invasiva

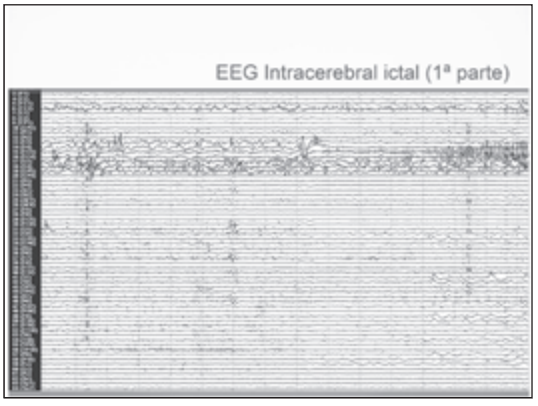
Mapeo funcional a partir de la Estimulación eléctrica cerebral

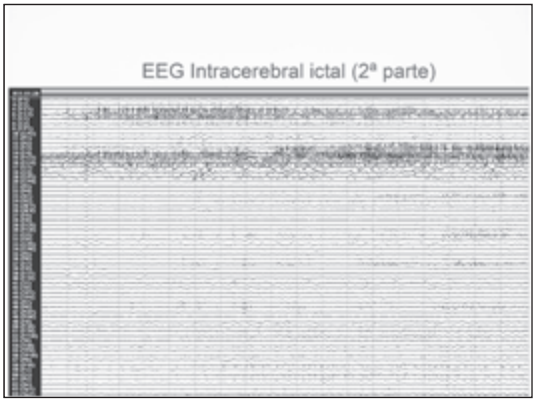
- **SS1° o AM 1°** Situación ideal paciente des en reposo.
- Respuesta habituales clónicas o sensaciones lin a distintas regiones anatómicas.
- Existe variabilidad en la extensión y tamaño de la corteza motora en mapeo extraoperatorio.
- **Lenguaje:** En zonas epileptógenas neocorticales temporales se deben incluir: Lectura, repetición, nominación y comprensión para optimizar la valoración del lenguaje.

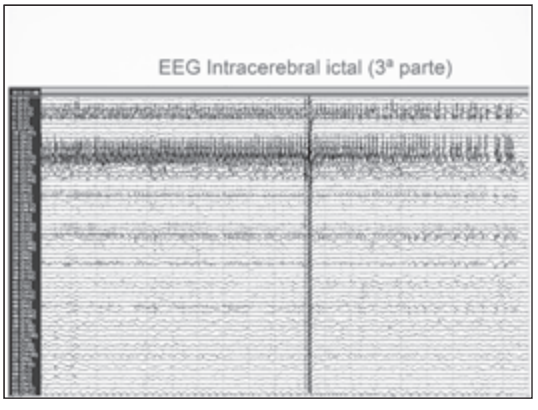


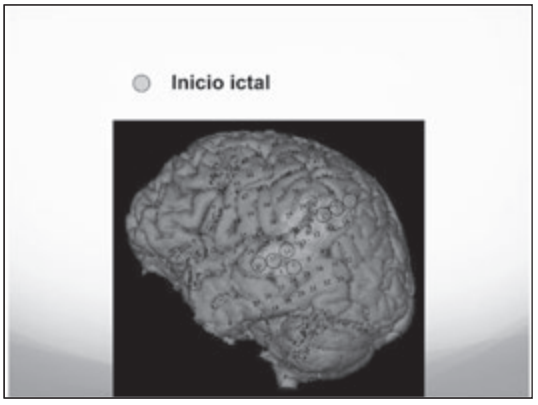
V-EEG Intracerebral (Crisis)


EEG Intracerebral ictal (1ª parte)


EEG Intracerebral ictal (1ª parte)

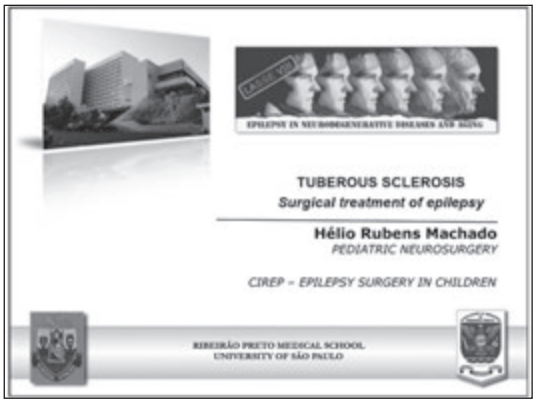

EEG Intracerebral ictal (2ª parte)

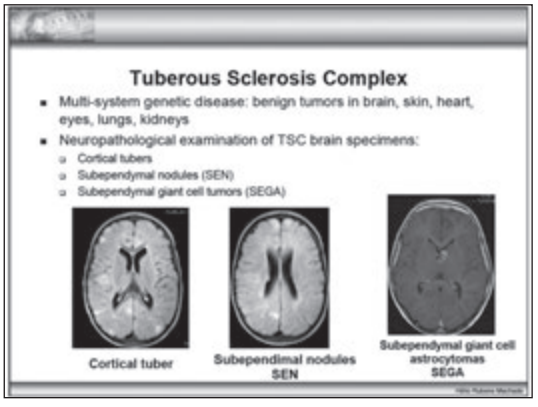

EEG Intracerebral ictal (3ª parte)

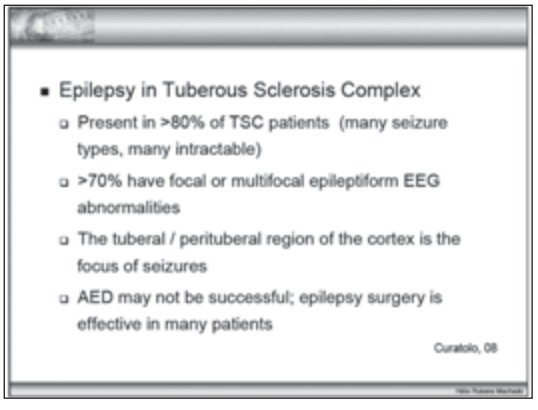

Inicio ictal

Hélio Rubens Machado (Brazil)

SURGERY IN TUBEROUS SCLEROSIS COMPLEX







- Epilepsy in Tuberous Sclerosis Complex
  - 63% of patients experience seizure onset in the 1st year of life
  - 38% have infantile spasms
  - Focal seizures may precede, coexist with or evolve into infantile spasms
  - The likelihood of developing epilepsy after a first seizure is 100%
  - Vigabatrin is the drug of choice in TSC-related Infantile spasms

Curatolo, 08

- Clinical characteristics
  - Symptomatic etiologies

1996 to 2012

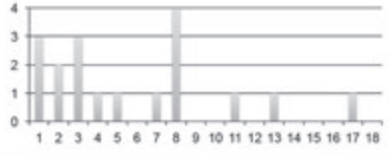
Children 409
Surgeries 443

TSC CHILDREN EVALUATED
total : 44 children
selected for surgery: 20 children

CIREP Children – Ribeirão Preto
UNIVERSIDADE DE SÃO PAULO
BRASIL

Pathology	
Cortical Dysplasia	130
Tumor	59
Gliosis	62
Mesial temporal sclerosis	48
Rasmussen encephalitis	28
Porencephaly	19
Tuberous sclerosis	20
Difuse atrophy	18
MR normal	9
Sturge-Weber	9
AVM	3
(other 4) Total	409

Age at surgery – 20 patients



DEFINING THE TARGET OF SURGERY
- Main objective identify epileptogenic tuber and evaluate benefits and risks of resection as early as possible

Patient management

SURGERY

ECoG	Invasive	none
8	10	2

INVASIVE EVALUATION
subdural / depth recordings

INTENSIVE VIDEO/EEG MONITORING
SPEC interictal / ictal
FDG PET / MEG - AMP-PET

Pharmacoresistance? Clinical evaluation
Localization hypothesis ?
MR screening

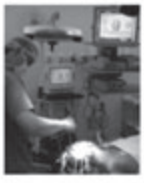
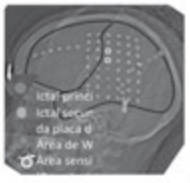
Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex

- UCLA – ictal video EEG localized to a quadrant in 39%, hemisphere in 36 %
- All patients FDG-PET and MRI + MSI
- 67% Sz free after surgery

Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with alpha-[11C]methyl-L-tryptophan positron emission tomography (PET).

- AMT PET detects dysplasia around tubers

- Surgical technique
  - Functional mapping
    - Intra-operative monitoring

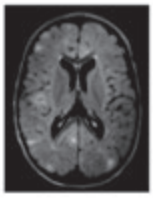
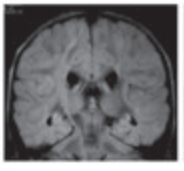
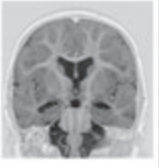



❑ Neuronavigation ❑ ECoG / invasive monitoring ❑ Brain stimulation

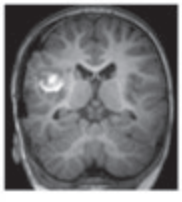
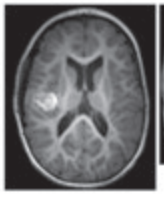
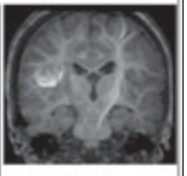
---

Tuberous Sclerosis

- ASRPF, 2 yo, sz since 6 mo old w eye blink and at 8 mo w head fall. TSC complex was diagnosed. Infantile spasms started at 11 mo age. Video-monitoring and invasive monitoring demonstrated sz starting at R insula

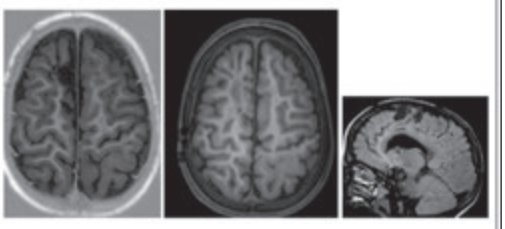




- Surgery: Resection of the tuber

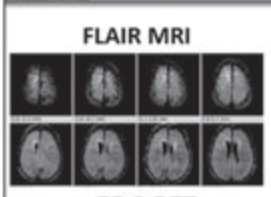
- Outcome: Seizure free. Mild L deficit (cleared 6 mo after surgery)

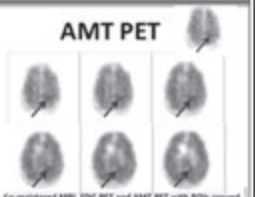
- PLT, 4 yo, TSC, submitted to surgery elsewhere, sz persisted.



FLAIR MRI

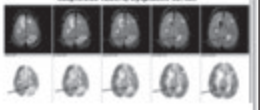
AMT PET





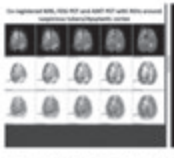
FDG PET

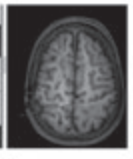
Co-registered MRI, FDG PET and AMT PET with ROIs around suspicious tubers/dysplastic cortex

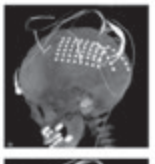


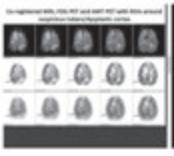
DMC Children's Hospital of Michigan

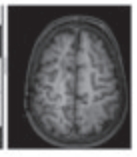
Harry T. Chugani, M.D.

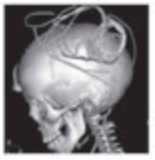




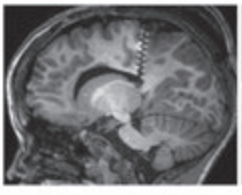


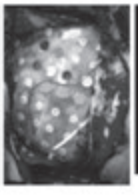


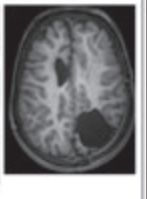




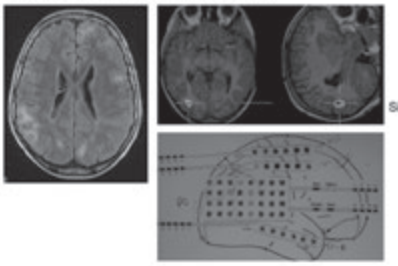
Invasive monitoring- grid and depth electrode. Engel I (1 year postop)





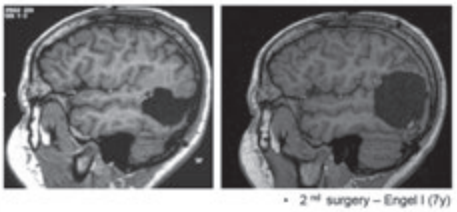


- FAFC, 7 yo. sz since 2 mo , Infantile Spasms



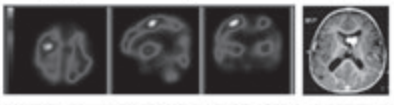
Siscom

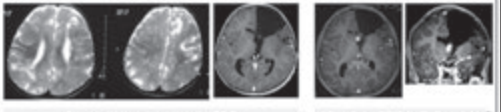
- 1st surgery – Lesionectomy . Sz persisted



- 2 nd surgery – Engel I (7y)

- JLBN, 1 year 5 mo, sz since 3 mo old, Infantile Spasms, developmental delay. Video-EEG : L frontal. Ictal SPECT: hiperperfusion L Frontal. Surgery:L Frontal lobectomy + resection of SEGA. Engel I (10 y fu).

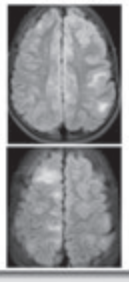


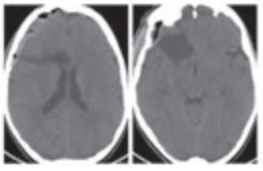


Surgical approaches in TSC

10 y fu – SEGA R Frontal

- JJBCF, 5 y old, sz since 6 mo age, refractory to AED, mild cognitive delay, TSC.

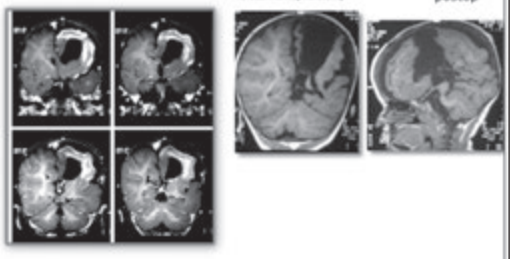




R Frontal Disconnection + resection of tuber Engel I

- FAPS,10 mo old, Infantile spasms, TSC (hemimegalencephaly). Engel I
- Vertical hemispherotomy

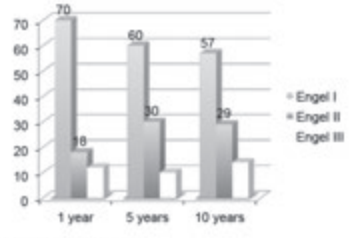
postop



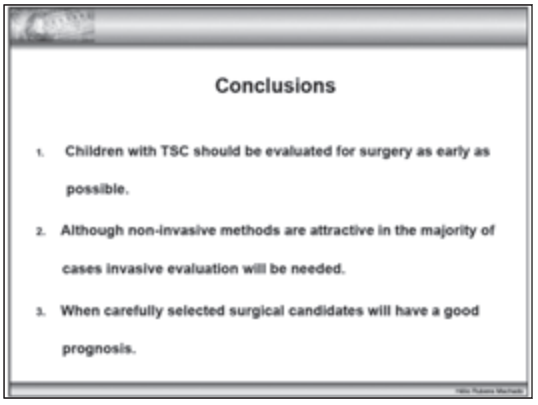
- **TSC Natural History Database Project: Epilepsy Surgery (Nakagawa J, AES,2009)**
  - 28% surgery (173 incl SEGA, VNS); 72% medical
  - Brain surgery (multiple procedures)
    - VNS 51%
    - Resective Surgery 49%
      - 28 % lesionectomies; multilobar resections 20%; hemispherectomy 2%
      - corpus callosotomy 7,5%
      - SEGA resection 22%

SURGICAL TECHNIQUES APPLIED TO TSC PATIENTS

Results of surgical treatment in TSC patients



- mortality – 1 case


Conclusions
1. Children with TSC should be evaluated for surgery as early as possible.
2. Although non-invasive methods are attractive in the majority of cases invasive evaluation will be needed.
3. When carefully selected surgical candidates will have a good prognosis.

Manuel Campos (Chile)

SURGERY IN FOCAL CORTICAL DYSPLASIAS

Mario Alonso (Mexico)

SURGERY IN PWE OLDER THAN 50 YEARS