SYLLABUS

TC01: Treatment of Epilepsy: An Update

Saturday, November 12, 2011 14:30-18:00 Hall I

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WCN Education Program

Saturday, 12 November, 2011

14:30-18:00

TREATMENT OF EPILEPSY: AN UPDATE

Chairperson: **Antonio Gil-Nagel**, *Spain*

BENIGN FOCAL EPILEPSIES OF CHILDHOOD
Natalio Fejerman, Argentina

EPILEPSY AFTER TRAUMATIC BRAIN INJURY
Alla Guekht, Russia

EPILEPSY IN THE ELDERLY
Antonio Gil-Nagel, Spain

16:00-16:30 Coffee Break

Benign Focal Epileptic Syndromes in Childhood

Dr. Natalio Fejerman
Department of Neurology
J. P. Garrahan Pediatric Hospital, Buenos Aires

- Benign childhood epilepsy with centrotemporal spikes (BCECTS)
  - *Atypical evolutions of BCECTS*
- Late-onset childhood occipital epilepsy (Gastaut type)
  - *Atypical evolutions of childhood occipital epilepsy (Gastaut type)*
- Panayiotopoulos syndrome
  - *Atypical evolutions of Panayiotopoulos syndrome*

Benign Childhood Epilepsy with Centro temporal Spikes (BCECTS)

Clinical Features

- Onset between 4 and 10 years of age in 80 to 90 % of cases
- Seizures during sleep in 85 to 90% of cases
- Features of seizures:
  - Orofacial motor signs
  - Speech arrest
  - Somatosensitive symptoms
  - Sialorrhea

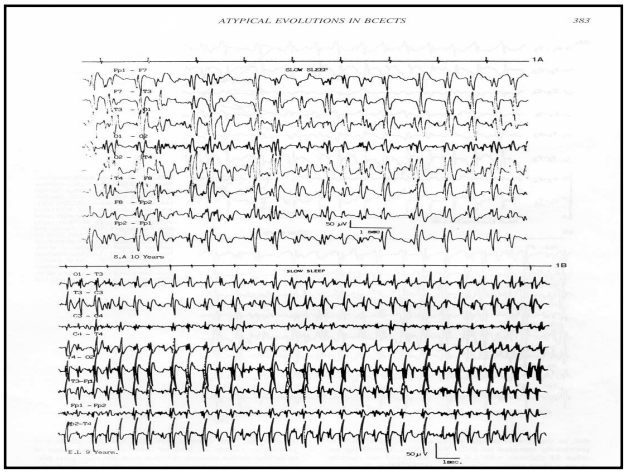
Benign Childhood Epilepsy with Centro temporal Spikes (BCECTS)

EEG Features

- Normal background activity.
- Typical EEG paroxysm: focal negative diphasic slow spike, of medium to high voltage, followed by a slow wave, located in the Rolandic or centrotemporal areas with possible difussion to the adjacent regions.
- Centrotemporal spikes significantly increase in frequency during drowsiness and through sleep.
- In approximately 30% of children centrotemporal spikes appear only during sleep.
- During evolution, 20 to 30% of children with BCECTS present brief discharges of generalized spike-waves.

Table 2 – Differential diagnosis between BCECTS and other epilepsy syndromes

- With symptomatic or probably symptomatic epilepsies
  - Mesial temporal lobe epilepsy
  - Symptomatic lateral temporal lobe epilepsy
  - Other focal epilepsies with seizures arising from neocortical areas
  - Symptomatic epilepsies arising from Rolandic - Sylvian areas
- With other idiopathic epilepsy syndromes
  - Benign infantile focal epilepsy with midline spikes and waves during sleep
  - Panayiotopoulos syndrome
  - Late-onset occipital lobe epilepsy (Gastaut type)
  - Other proposed benign focal epilepsy syndromes
  - Autosomal dominant partial epilepsy with auditory features
  - Autosomal dominant rolandic epilepsy with speech dyspraxia



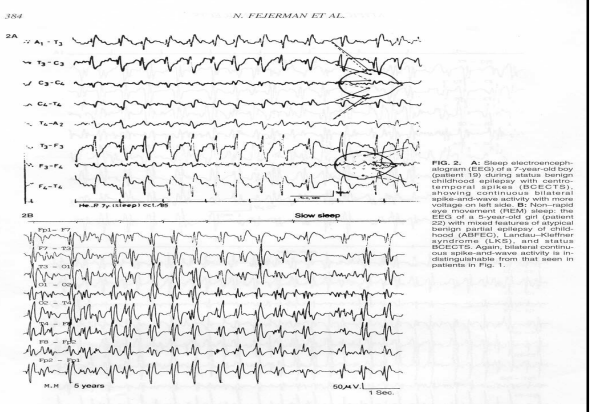


FIG. 2. A: Sleep electroencephalogram (EEG) of a 7-year-old boy (patient 19) during stable benign partial epilepsy of childhood with centrotemporal spikes (BCECTS), showing continuous bilateral spike-and-wave activity with more voltage on left side. B: Non–rapid eye movement (NEM) sleep; the EEG of a 5-year-old girl (patient 22) with mixed benign focal benign partial epilepsy of childhood (ABFEC), Landau–Kleffner syndrome (LKS), and status BCECTS. Again, bilateral continuous spike-and-wave activity is indistinguishable from that seen in patients in Fig. 1.

Table 6 – Neuropsychological data on follow-up of 39 patients with atypical evolutions of BCECTS

Types of atypical evolutions	Number of Patients	Residual language impairment (Nr. of Patients)	Residual cognitive deficits (Nr. of Patients)	Residual behavior abnormalities (Nr. of Patients)	Mental retardation (Nr. of Patients)
ABFEC	16	–	–	–	–
Status of BCECTS	10	–	1 mild learning disorder	–	–
LKS	4	2	2 *	–	2 mild *
CSWSS	5	3	3 *	2 patients *	2 moderate * 1 mild *
Mixed forms of atypical evolutions	4	2	1 moderate * 1 mild *	1 moderate * 1 mild *	1 moderate * 1 mild *

ABFEC: Atypical benign focal epilepsy of childhood; BCECTS: Benign childhood epilepsy with centrotemporal spikes; LKS: Landau Kleffner syndrome; CSWSS: Continuous spike-and-waves during slow sleep syndrome
* the same as with language impairment.

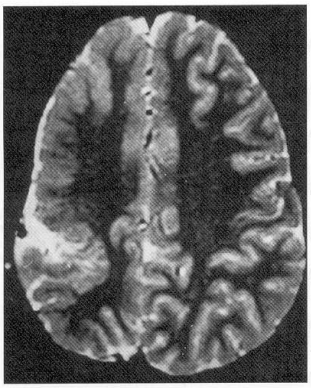


FIG. 2. Magnetic resonance imaging: T_2-weighted sequence showing right hemisphere atrophy with right frontoparietal cortical abnormality. Polymicrogyria was pathologically demonstrated.

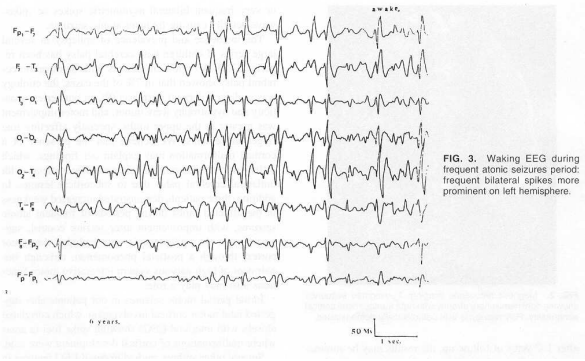


FIG. 3. Waking EEG during frequent atonic seizures period; frequent bilateral spikes more prominent on left hemisphere.

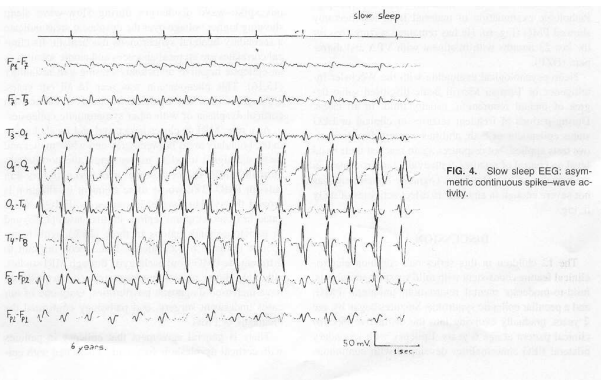


FIG. 4. Slow sleep EEG: asymmetric continuous spike–wave activity.

Table 1: differential diagnosis between COE "Gastaut type" and symptomatic occipital lobe epilepsies

-MELAS disease
-Lafora disease
-Celiac disease and epilepsy
-Occipital lobe epilepsy after neonatal hypoglycemia
-Sturge-Weber disease (without facial angioma)
-Periventricular leukomalacia and epilepsy
-Posterior periventricular nodular heterotopia
-Reversible posterior encephalopathy
-Chemotherapy, radiotherapy, occipital tumors, vasculitis, demyelination, others

Epilepsia Idiopática Occipital de la Niñez tipo Gastaut (EION Tipo Gastaut)

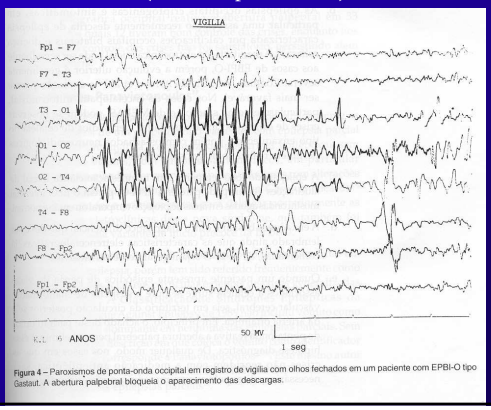


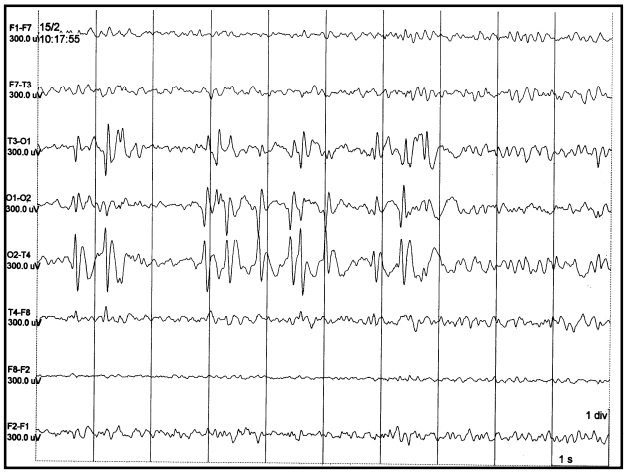
Figura 4 – Paroxismos de ponta-onda occipital em registro de vigília com olhos fechados em um paciente com EPBI-O tipo Gastaut. A abertura palpebral bloqueia o aparecimento das descargas.

Frequency of seizure types in children with Panayiotopoulos syndrome. Table 1.

Core clinical features
- Ictal emetic symptoms and other autonomic manifestations
- Deviation of the eyes
- Impairment of consciousness

Frequent types of seizures
- Unilateral clonic or tonic-clonic seizures
- Secondary generalized tonic-clonic seizures
- Encephalopathy-like status epilepticus (focal motor –unilateral or generalized- and autonomic)

Less frequent – but not rare – symptoms and signs
- Visual symptoms
- Migraine-like headaches
- Incontinence of urine and faeces
- Syncope-like symptoms
- Other



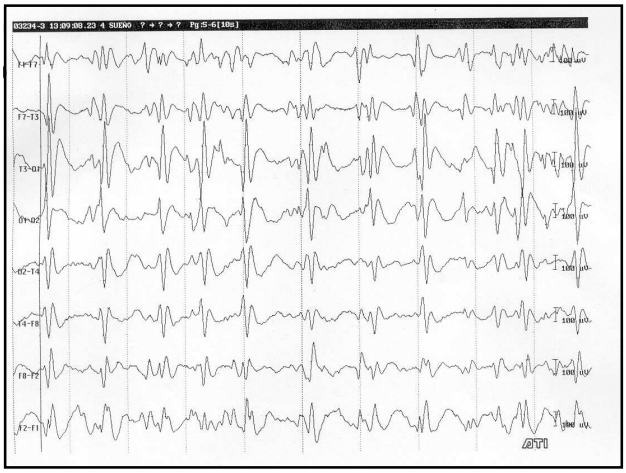
Differential diagnosis of Panayiotopoulos syndrome. Table 2.

With other neurological conditions

- Encephalitis
- Acute toxic encephalopathy
- Acute disseminated encephalomyelitis (ADEM)
- Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
- Acute cerebrovascular event
- Migraine (basilar artery migraine)
- Diseases of the autonomic nervous system

With other epilepsy syndromes

- With other idiopathic epilepsy syndromes
- Childhood epilepsy with occipital paroxysms (Gastaut type)
- Benign childhood epilepsy with centrotemporal spikes
- Idiopathic photosensitive occipital epilepsy
- With symptomatic occipital epilepsies
- Celiac disease, occipital calcifications and epilepsy
- Occipital epilepsy after neonatal hypoglycemia
- Other symptomatic occipital epilepsies



Proposed scheme of treatment

A) How to prevent the atypical evolutions of BFEC

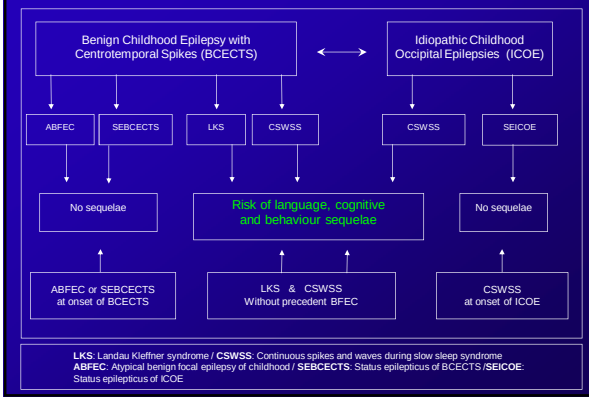
- After considering the risk factors, the recommendations to prevent atypical evolutions may be:

1. Avoid the use of classic AEDs (PB, PH, CMZ, VA) and some of the new AEDs (LTG, OXC, GBP) in patients with BFEC presenting atypical clinical features and/or excessive EEG abnormalities
2. When these risks are evident, start treatment with Sulthiame or Benzodiazepines
3. In patients with BFEC with clear generalized spike-wave discharges, VA may be a good chance. It is also the first choice in patients with the Gastaut type of CEOP
4. In patients without the mentioned risks and presenting seizures only during night sleep, we recommend single doses of Clobazam at night
5. Finally, a good alternative to discuss with parents in these patients without risks, is not to use medication

B) Treatment strategies in children with any of the epileptic encephalopathies with ESES, including the symptomatic cases

1. Start discontinuation of the AED that the patient is taking and introduce Benzodiazepines, Ethosuximide (ETS), or Sulthiame.(SLT). A combination of two of these may also be used.
2. If no significant improvement is seen, the following indication is steroids in high doses.
3. We reported on one case of status of the Gastaut type of CEOP who only responded to intravenous immunoglobulins (Fejerman et al. 1991, Tenembaum et al. 1997), and several cases with successful use of immunoglobulins in patients with LKS were also reported (Fayad et al. 1997, Lagae et al. 1998, Mikati et al. 2002).
4. We have already commented on the reported cases of LKS who underwent successful subpial transections (Morrell et al. 1992, 1995, Irwin et al. 2001) and Vagal nerve stimulation (Park 2003).

Figure 12. Benign focal epilepsies of childhood (BFEC) and disorders related with ESES



EPILEPSY AFTER TRAUMATIC BRAIN INJURY

A.B.Guekht

Russia

Traumatic brain injury accounts for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy

Hauser WA, Annegers JF, Kurland LT. *Epilepsia* 1991;32:429–445.

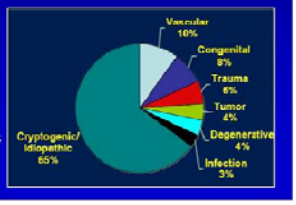
Approximately 1.4 million people sustain a TBI each year in the United States. Of those:

- 50,000 die;
- 235,000 are hospitalized; and
- 1.1 million are treated and released from an emergency department.

Langlois JA et al. 2004.

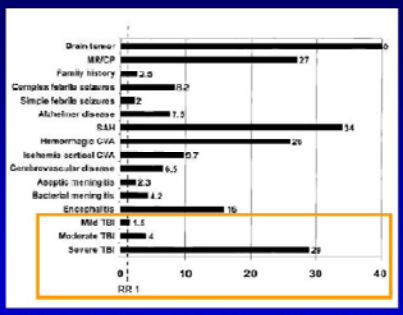
The Incidence of Epilepsy after TBI

- Ranges from 1.9% to over 30%, the magnitude of risk being dependent on the severity of trauma and the duration of follow-up
- In civilian populations, the overall risk is estimated at 2–5%, increasing to 7–39% for subgroups with cortical injury and neurologic sequelae.



Frey LC. Epilepsia 2003; 44 (Suppl 10):11–17.
Annegers JF, Hauser WA, Coan SP, et al. NEJM 1998; 338:20–42.
Beghi E. Epilepsia 2003; 44 (Suppl 10):21–26.
D'Ambrosio R., Perucca E. Curr Opin Neurol , 2004. 17,731–735.

Relative Risk for Unprovoked Seizures after Common Brain Injuries



The dotted vertical line represents the general population risk for unprovoked seizures

Forsgren L. Epilepsia 1990;31:292–301.

Definitions

- PTE is one or more unprovoked seizures occurring late (e.g. at least 1 week) after TBI, the latter being defined as head trauma requiring some degree of medical attention (Frey, 2003).
- 1 or at least 2 late seizures?

- Although in a strict sense a diagnosis of epilepsy should be limited to patients with at least two unprovoked seizures, a broader defnition is justifable because many PTE studies limited their follow-up to occurrence of only one seizure (D'Ambrosio R., Perucca E, 2004)

- 86% of patients with one late posttraumatic seizure had a second seizure within 2 years (Haltiner AM, et al., 1997).

- Early posttraumatic seizures are defned as seizures occurring within 7 days of trauma.
- Seizures occurring within minutes of the impact are not usually included in studies of early posttraumatic seizures.

Incidence of Early and Late Posttraumatic Seizures in Civilian Populations

Study	Feature	N	Early Seizure %	Risk Factors	Late Seizure %	Risk Factors
Jennett and Lewin (3)	Admitted	896	4.2	PTA > 24h, age <5y, skull fracture, intracranial hemorrhage	10.2	Early seizure, PTA > 24h, depressed skull fracture, intracranial hematoma
Annegers et al. (2)	Population	2747	2.1	Age <15 y, severe injury	1.9	Severe injury, early seizure
Desai et al. (4)	Admitted, pediatric	702	4.1	Age < 16 y, focal neuro deficits, LOC/PTA >30 min, skull fracture, intracranial hematoma	N/A	N/A
Annegers et al. (5)	Population	4541	2.6	Not evaluated	2.1	Severe injury, brain contusion, subdural hematoma, LOC/PTA >24h
Hahn et al. (6)	Admitted, pediatric	937	9.8	GCS 3–8, diffuse cerebral edema, acute subdural hematoma	N/A	N/A
Angeleri et al. (7)	Admitted	137	8		13.1	GCS 3–8, early seizures, single brain CT lesions, EEG focus
Asikainen et al. (8)	TBI Rehab Center	490	16.3	Age <8 y	25.3	Early seizures, depressed skull fracture
Englander et al. (9)	Admitted with CT findings or GCS 3–10	647	3	N/A	10.2	Multiple or bilateral cortical contusions, dural penetration, multiple intracranial operations, midline shift >5mm, evacuated SDH

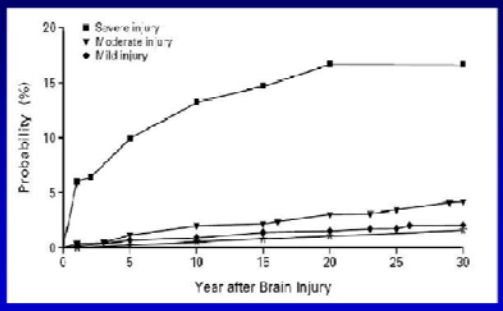
Garga N., Lowenstein D.Epilepsy Currents, Vol. 6, No. 1 2006 pp. 1–5

Early Seizures after TBI
Acute symptomatic seizures

- Acute symptomatic seizures are seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult
- Acute symptomatic seizures differ from unprovoked seizures in terms of mortality and recurrence and can be considered risk factors for unprovoked seizures and epilepsy but not symptoms of epilepsy per se.

Commission on Epidemiology and Prognosis, ILAE, 1993 ; Hesdorffer et al. 2009; Beghi, 2010.

Cumulative Probability of Unprovoked Seizures in 4,541 Patients with TBI



Annegers et al. N Engl J Med 1998; 338:20–42

Risk of Seizures over Time

- In most cases of PTE, risk is highest in the first year after trauma, and decreases progressively thereafter.
- How long an increased risk persists is a matter of controversy.
- **In a population-based study (Annegers et al., 1988), persons with**
  - **moderate injury continued to have an increased risk for up to 10 years, whereas**
  - **those with severe injuries had an increased risk for over 20 years after injury**

Posttraumatic Epilepsy: Risk Factors

- Acute intracerebral hematoma (especially subdural hematoma)
- Brain contusion
- Increased injury severity (as refected by LOC or posttraumatic amnesia for 24 h)
- Occurrence of early posttraumatic seizures
- Being older than 65 years at the time of injury

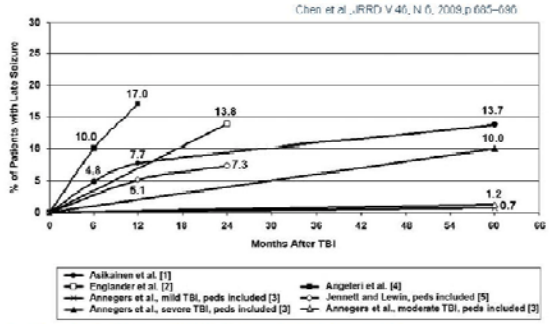
Frey LC. Epilepsia 2003; 44 (Suppl 10):11–17.

Rate Ratios for Seizures after TBI

Variable	Traumatic Brain Injuries	Late Seizures	Rate Ratio (95% CI)†		
			Univariate	Model 1	Model 2
	no. of patients				
Brain contusion or subdural hematoma	87	18	30.8 (16.6–55.2)	11.3 (4.7–27.3)	12.1 (5.2–28.2)
Brain contusion only	159	19	8.9 (5.3–14.8)	5.0 (2.5–10.0)	5.0 (2.6–9.8)
Subdural hematoma only	36	4	9.8 (3.6–27.1)	6.3 (2.2–18.0)	6.7 (2.3–19.1)
Linear fracture and age ≥5 yr or depressed fracture	527	35	4.1 (2.7–6.2)	—	2.0 (1.2–3.2)
Linear fracture and age ≥5 yr	313	17	3.3 (1.9–5.6)	2.2 (1.3–3.8)	—
Depressed fracture	214	18	5.2 (3.1–8.9)	1.8 (0.94–3.3)	—
Loss of consciousness or post-traumatic amnesia for more than 24 hr	176	24	8.4 (5.3–13.3)	1.9 (0.97–3.6)	1.9 (0.98–3.5)
Early seizure	117	12	5.5 (3.0–10.1)	1.4 (0.7–2.7)	—
Age ≥65 yr	269	10	2.5 (1.3–4.9)	2.2 (1.1–4.4)	2.2 (1.1–4.4)

Annegers et al. N Engl J Med 1998; 338:20–42

Cumulative probability of late unprovoked seizures after traumatic brain injury (TBI) in seven studies.



- Mild to moderate TBI is correlated with lower risk of developing (PTE).
- Prevalence of PTE was 10 to 17 percent with maximal follow-up period of 5 years.

Factors Associated with the Highest Cumulative Probability for PTE over a 2-year Follow-up

Prospective multicenter study, which enrolled 637 patients with moderate to severe TBI

- biparietal contusions (66%)
- dural penetration with bone and metal fragments (62.5%)
- multiple intracranial operations (36.5%)
- multiple subcortical contusions (33.4%)
- subdural hematoma with evacuation (27.8%),
- midline shift greater than 5 mm (25.8%), or multiple or bilateral cortical contusions (25%)

Englander J, Bushnik T, Duong TT, et al.. Arch Phys Med Rehabil 2003; 84:365–373.

The pathology associated with TBI

Primary injury

- Associated with the initial mechanical insult, resulting in immediate and often irreversible damage to neuronal cell bodies, dendrites, axons, glial cells, and brain vasculature.
- Tissue deformation and compression, leading to seizures, respiratory depression, apnea,ischemic, and hypoxic damage resulting in cellular injury

(Bramlett and Dietrich, 2004; Gaetz, 2004).

The Pathology Associated with TBI

Secondary injury.

Caused by an incompletely understood and complex cascade of physiological and biochemical factors continuing for hours to days post-injury that results in progressive tissue damage

Tissue necrosis and progressive neuronal cell death occur within and outside of immediately damaged areas.

Secondary damage from hypoxia– ischemia, edema, and breakdown of the blood–brain barrier may also occur

Halliday AL, 1999; Bramlett and Dietrich, 2004; Gaetz, 2004; Thompson et al., 2005.

Epilepsia, 46(6):872–1011, 2005
Blackwell Publishing, Inc.

Predicting Posttraumatic Epilepsy with MRI: Prospective Longitudinal Morphologic Study in Adults

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*Department of Neuroradiology, Umberto I Hospital and University of Ancona, and †Department of Epidemiology, Biostatistic and Medical Informatics Technologist, University of Ancona, Ancona, Italy

Summary: *Purpose:* Evaluation of morphologic risk factors for posttraumatic epilepsy (PTE) by using brain magnetic resonance imaging (MRI) in serial assessments ≤2 years after traumatic brain injury (TBI).

Methods: Brain MRI hyperintense (gliosis) or hypointense (hemosiderin) areas or both were assessed in the images of 155 adult TBI inpatients who completed a 2-year clinical, EEG, and MRI study protocol. Overall clinical follow up for the development of PTE was 5–10 years (median, 102 months). Morphologic risk factors for PTE were evaluated by using Kaplan–Meier curves and Cox regression analysis.

Results: In 20 patients, PTE developed. Kaplan–Meier curves showed that gliomesenchymal sequelae of focal brain lesions (subdural hematomas/contusions) that required surgical treatment (sSDH-C) were a PTE risk factor ($p < 0.001$), as were sequelae of nonsurgical hemorrhagic contusions with gliosis wall incompletely surrounding hemosiderin dregs (IW) ($p = 0.039$) and mainly those with time-related changes from incomplete to complete gliosis wall around hemosiderin (I/CW) ($p = 0.005$), those with early hemosiderin completely surrounded by gliosis (CW) were not ($p = 0.821$). Cox regression analysis showed that for patients with sequelae of sSDH-C, the PTE risk was 4.58 ($p = 0.023$) times higher than for those who did not require surgical treatment or underwent surgery because of purely extradural hematoma; for those with IW and I/CW lesions, considered pooled, it was 6.61 times higher ($p = 0.014$) than for those with CW lesions.

Conclusions: MRI follow-up examination in the early chronic stage can differentiate among low-, intermediate-, and high risk sequelae of TBI. These findings yield new evidence for, but do not resolve, the debate on posttraumatic epileptogenesis. **Key Words:** Posttraumatic epilepsy—Brain MRI—Hemosiderin—Gliosis.

Predicting Posttraumatic Epilepsy with MRI: PTE Risk Factors

- Gliomesenchymal sequelae of focal brain lesions (subdural hematomas/contusions) that required surgical treatment (sSDH-C) ($p < 0.001$),

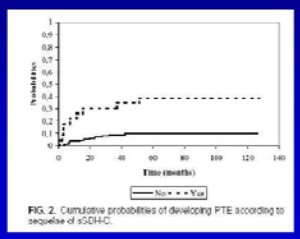


FIG. 2. Cumulative probabilities of developing PTE according to sequelae of sSDH-C.

Messori et al., 2005

Predicting Posttraumatic Epilepsy with MRI: PTE risk factors

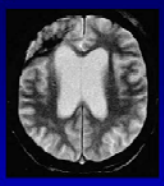
- Gliomesenchymal sequelae of focal brain lesions (subdural hematomas/contusions) that required surgical treatment (sSDH-C) ($p < 0.001$)
- Sequelae of nonsurgical hemorrhagic contusions with gliosis wall incompletely surrounding hemosiderin dregs (IW) ($p = 0.039$)
- Mainly those with time-related changes from incomplete to complete gliosis wall around hemosiderin (I/CW) ($p = 0.005$);

Those with early hemosiderin completely surrounded by gliosis (CW) were not of increased risk ($p = 0.821$).

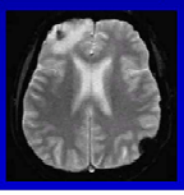
Messori et al., 2005

Predicting Posttraumatic Epilepsy with MRI: PTE risk factors

- Sequelae of nonsurgical hemorrhagic contusions with gliosis wall incompletely surrounding gemosiderin dregs (IW) (p = 0.039)



- Those with early hemosiderin completely surrounded by gliosis (CW) were not of increased risk (p = 0.821).



Messori et al., 2005

ORIGINAL CONTRIBUTION

Increased Risk of Late Posttraumatic Seizures Associated With Inheritance of *APOE* ε4 Allele

Ramon Diaz-Arrastia, MD, PhD; Yunhua Gong, MD; Sargyne Fair, BA; Kristin D. Scott, BA; Maria C. Garcia, MD; Mary C. Castillo, MD; Mark A. Agostini, MD; Paul C. Van Ness, MD

Background: Late posttraumatic seizures are a common complication of moderate and severe traumatic brain injury. Inheritance of the apolipoprotein E (*APOE*) ε4 allele is associated with increased risk of Alzheimer disease, progression to disability in multiple sclerosis, and poor outcome after traumatic brain injury.

Objective: To determine whether inheritance of *APOE* ε4 is associated with increased risk of developing late posttraumatic seizures.

Design: Prospective study.

Setting: Neurosurgical service at an urban level I trauma center.

Patients: Patients admitted with a diagnosis of moderate and severe traumatic brain injury were enrolled.

Methods: Six months after injury, patients were contacted to determine functional outcome (according to the Glasgow Outcome Scale–Expanded [GOS-E]) and the presence of late posttraumatic seizures. Genotype at the *APOE* locus was determined by restriction fragment length polymorphism analysis.

Results: DNA and outcome information was obtained from 106 subjects. Six months after injury, 31 (29%) had a poor outcome (GOS-E score, 1–4), 47 (44%) had an intermediate outcome (GOS-E score, 5–6), and 28 (26%) had a favorable outcome (GOS-E score, 7–8). Twenty-one patients (20%) had at least 1 late posttraumatic seizure. The relative risk of late posttraumatic seizures for patients with the ε4 allele was 2.41 (95% confidence interval, 1.13–5.07; $P = .03$). In this cohort, inheritance of *APOE* ε4 was not associated with an unfavorable GOS-E score ($P = .47$).

Conclusions: Inheritance of the *APOE* ε4 allele is associated with increased risk of late posttraumatic seizures. In this cohort, this risk appears to be independent of an effect of ε4 on functional outcome. A better understanding of the molecular role of *APOE* in neurodegenerative diseases may be helpful in developing antiepileptogenic therapies.

Arch Neurol. 2003;60:808-822

Cellular Mechanisms of Posttraumatic Epileptogenesis

- In-vitro model of stretch injury (reproduces a mechanical component of concussive head injury):
  - alterations in glutamatergic transmission mediated by AMPA receptors
  - loss of desensitization of the AMPA receptor, with consequent potentiation of AMPA - mediated synaptic transmission in cultured cortical potentiation

(These events occurs within 15–30 min following injury, persists for 24 h)

- Stretch injury of cortical neurons in culture also results in modifcation of GABA A transmission as early as 15 min–7 h after the injury

Goforth PB, Ellis EF, Satin LS. . J Neurotrauma 2004; 21:719–732.
Kao CQ, Goforth PB, Ellis EF, Satin LS. J Neurotrauma 2004; 21:259–270.

Cellular Mechanisms of Posttraumatic Epileptogenesis

Specific changes in both excitatory and inhibitory synapses occur after stretch injury and may represent novel therapeutic targets to be investigated in in-vivo models.

A temporal window during which these synaptic changes occur and are maintained, and therefore suggest the duration of the critical period during which antiepileptogenic prophylaxis may be attempted.

D'Ambrosio R., Perucca E. Curr Opin Neurol, 2004 17:731–735

Diagnosis and Treatment

- Epilepsy is a clinical diagnosis!
- EEG - Useful for localization of focus, but not shown to be helpful in predicting post-TBI patients at risk
- CT - Focal hemorrhagic injury strong predictor (D'Alessandro et al. JNNP 45:1153, 1982)
- MRI - Hemosiderin deposits and gliotic scar shown by T2-weighted imaging may be a predictor (Kumar et al. Am J Neurorad 23:218, 2003)

- Prophylactic use of AEDs should be short-lasting and limited to the prevention of immediate and early seizures.
- Chronic treatment should be considered only after a diagnosis of PTE

AEDs for Preventing Seizures following Acute Traumatic Brain Injury

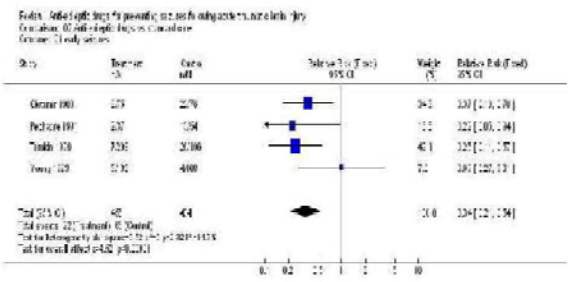
The Cochrane Database of Systematic Reviews.

MAIN RESULTS: Identified 10 eligible randomised controlled trials, including 2036 participants, but data was unavailable for four unpublished trials, representing 631 participants and they were excluded

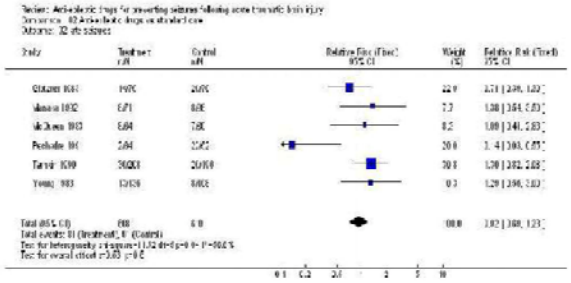
For the remaining six trials:

- **The pooled relative risk (RR) for early seizure prevention was 0.34 (95%CI 0.21, 0.54);**
- Seizure control in the acute phase was NOT accompanied:
  - **by a reduction in mortality (RR = 1.15; 95%CI 0.89, 1.51),**
  - **a reduction in death and neurological disability (RR = 1.49; 95%CI 1.06, 2.08 for carbamazepine and RR = 0.96; 95%CI 0.72, 1.26 for phenytoin)**
  - **or a reduction in late seizures (pooled RR = 1.28; 95%CI 0.90, 1.81).**
- The pooled RR for skin rashes was 1.57 (95%CI 0.57, 39.88).

ANTI-EPILEPTIC DRUGS VS STANDARD CARE
early seizures.



ANTI-EPILEPTIC DRUGS VS STANDARD CARE
late seizures.



AEDs for Preventing Seizures following Acute Traumatic Brain Injury
The Cochrane Database of Systematic Reviews.

CONCLUSIONS:

Prophylactic AEDs are effective in reducing early seizures, but

there is no evidence that treatment with prophylactic AEDs reduces the occurrence of late seizures, or has any effect on death and neurological disability.

Insufficient evidence is available to establish the net benefit of prophylactic treatment at any time after injury.

AED in TBI

According to the AAN guidelines (2003), for adult patients with severe TBI (with prolonged loss of consciousness or amnesia, intracranial hematoma or brain contusion, and/or depressed skull fracture):

- Prophylactic treatment with PHT, beginning with an IV loading dose, should be initiated as soon as possible after injury to decrease the risk of posttraumatic seizures occurring within the first 7 days (Level A).
- Prophylactic treatment with PHT, CBZ, VPA should not routinely be used beyond the first 7 days after injury to decrease the risk of post-traumatic seizures occurring beyond that time (Level B).

Why has AEDs Prophylaxis Failed to Protect against Late Posttraumatic Seizures?

The AEDs tested were intrinsically devoid of antiepileptogenic properties

The AEDs most frequently investigated in PTE trials, for example PHT and CBZ, show little or no protective activity in animal models of epileptogenesis (Loscher W.2002) and would not represent the best choice if a human trial were to be set up today (Schmidt D, Rogawski M. 2002)

Potential benefit of LEV, VPA, TPM, PGB, LCS .....
..... to be investigated

D'Ambrosio R , Perucca E. Curr Opin Neurol 17:731–735

Neuroprotective effects of AEDs in experimental models

Antiepileptic drugs	Neuroprotection in Ischemia	Neuroprotection against convulsants or convulsive procedures	Induction of neurodegeneration
Felbamate	+	+	ND
Gabapentin	+	+	ND
Levetiracetam	+/–	–	ND
Losigamone	ND	+	ND
Oxcarbazepine	+/–	+/–	+
Pregabalin	ND	ND	ND
Remacemide	+	+	ND
Talampanel	+	+	+
Tiagabine	+	+/–	+
Topiramate	+	+	+*
Vigabatrin	+	+/–	+
Zonisamide	+	ND	ND

Stepien et al., 2005

AEDs mechanisms of action

	VOC Na blockade	VOC Ca blockade	GABA enhancement	Glutamate antagonism	Other actions
BDZ	-	-	++	-	-
CBZ	++	+ (L)	?	+(NMDA)	+
ETX	-	++(T)	-	-	-
FLB	++	+(L)	+	++(NMDA)	+
GBP	-	++ (N, P/Q)	+?	-	+?
LEV	-	+ (N)	+	?	++
LTG	++	++ (N, P/Q, R, T)	+	++(NMDA, AMPA)	+
OXCBZ	++	+ (N, P)	?	+(NMDA)	+
PGB	-	++ (N, P/Q)	-	-	-
PHR	-	?	+	-	+
PHT	++	?	-	?	+
TGB	-	-	++	-	-
TPM	++	+ (L)	+	++(AMPA)	+
VGB	-	-	++	-	-
VPA	?	+ (T)	+	+(NMDA)	++
ZNM	++	++ (N, P, T)	?	-	+

+ secondary action; ++ primary action; - not described; ? controversial; VOC: voltage opened channel.

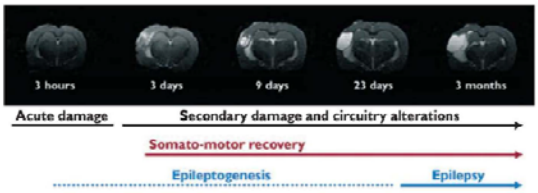
Mula and Monaco, 2008

Effects of administration of antiepileptic drugs on posttraumatic recovery in experimental models

AED	Beginning and duration of treatment	Outcome measures (time of analysis)	Effect	Reference
Remacemide	15 min postinjury Rx single dose	Cortical lesion (48 h postinjury) Learning and memory (48 h postinjury)	↓ ⇔	Smith et al. (1997b)
Topiramate	30 min postinjury Rx for 32 h	Edema (48 h postinjury) Neurodegeneration (48 h postinjury) Memory (48 h postinjury) Learning (4 weeks postinjury) Motor recovery (4 weeks postinjury) Rotating pole (4 weeks postinjury)	⇔ ⇔ ⇔ ↓ ↑ ↑	Hoover et al. (2004)
Talampanel	30 min postinjury Rx for 3 day	Cortical lesion (7 days postinjury) CA1 degeneration (7 days postinjury)	↓ ↓	Belayev et al. (2001)
Lacosamide	30 min postinjury Rx for 3 day	Lesion severity (2 weeks postinjury) Motor function (2 weeks postinjury) Learning and memory (2 weeks postinjury)	⇔ ⇔ ⇔	Nissinen et al. (2006)
Carisbamate (RWJ-333369)	15 min postinjury Rx for 1 day	Edema (48 h postinjury) Lesion size (4 week postinjury) Motor function (up to 4 week postinjury) Learning (4 week postinjury)	⇔ ⇔ ⇔ ⇔	Keck et al. (2007)

AED, antiepileptic drug.

TBI: recovery vs epileptogenesis



The brain faces many challenges after traumatic brain injury (TBI). Acute damage related to the primary impact is followed by a myriad of secondary molecular and cellular changes, including delayed neurodegeneration, neurogenesis, axonal injury, axonal sprouting, gliosis, and angiogenesis. Many of these alterations are apparently needed for successful recovery that occurs over the weeks and months postinjury. In parallel to the recovery process, a subpopulation of animals undergo epileptogenesis, culminating in the occurrence of spontaneous seizures. The great challenge is to differentiate those mechanisms that lead to favorable and unfavorable recovery.

TBI: recovery vs epileptogenesis

Acute damage → Secondary damage and circuitry alterations

AEDs : negative impact on recovery

- PHT, PB, BZD :
  - alter or delay functional recovery in animal models of stroke or brain damage (Brailowsky,1986; Schallert,1986)
  - negatively influence functional outcome in stroke patients (Goldstein,1990; 1995)

Effects of AEDs on acute symptomatic seizures

Type of injury	Drug	Relative risk	95% CI
Febrile seizures	DZP	0.71	0.44 – 1.13
	VPA	0.74	0.24 – 2.23
	PB	0.51	0.32 – 0.82
Traumatic brain injury	PB	0.30	0.03 – 2.81
	PHT	0.33	0.19 – 0.59
	CBZ	0.39	0.17 – 0.92
Malaria	PB	0.36	0.23 – 0.56
Asphyxia	PB	0.69	0.44 – 1.08
Alcohol	VPA	0.20	0.44 – 1.13
	PHT	0.70	
Contrast media	DZP	0.10	0.01 – 0.79
Brain tumor	PB	0.40	0.10 – 1.64
Craniotomy	PHT	0.42	0.25 – 0.71

Source: Temkin [2001].
Relative risk, ratio between the probability of occurrence of acute symptomatic seizures in patients receiving treatment and that of the control group; CBZ, carbamazepine; DZP, diazepam; PB, phenobarbital; PHT, phenytoin; VPA, valproate; CI, confidence interval.

Beghi, 2010

Effects of AEDs on late (unprovoked) seizures

Type of injury	Drug	Relative risk	95% CI
Febrile seizures	DZP	0.76	0.24 – 2.44
	PB	2.69	0.82 – 8.90
Traumatic brain injury	VPA	1.28	0.76 – 2.16
	PB	0.98	0.48 – 2.04
	PHT	0.70	0.33 – 1.50
	CBZ	0.79	0.42 – 1.49
Brain tumor	VPA	1.44	0.70 – 2.96
	PB	0.62	0.12 – 3.19
	PHT	0.80	0.42 – 1.52
Craniotomy	PHT	0.92	0.59 – 1.45
	CBZ	1.30	0.75 – 2.25

Source: Temkin [2001].
Relative risk, ratio between the probability of occurrence of acute symptomatic seizures in patients receiving treatment and that of the control group; CBZ, carbamazepine; DZP, diazepam; PB, phenobarbital; PHT, phenytoin; VPA, valproate; CI, confidence interval.

Beghi, 2010

Conclusions

- Traumatic brain injury accounts for 20% of symptomatic epilepsy in the general population and 5% of all epilepsy
- Definitions of early and late seizures, and epilepsy after TBI should be observed
- Early seizures after TBI are the risk factor for late aeizures and epilepsy after TBI
- Risk of seizures is the highest in the first year after trauma and decreases progressively thereafter However, seizures may appear many years after TBI
- Risk is increased after severe TBI, cases with acute intracerebral hematoma (especially subdural hematoma), brain contusion

Conclusions

- PHT and CBZ suppress early seizures, but none of the tested regimens show a positive effect on late.
- There is no evidence of antiepileptogenic or disease modifying effects of any of the AEDs.
- The AED treatment with PHT and CBZ, known to prevent early seizures, is usually associated with a number of adverse effects, including the impact on cognition, that is especially undesired in TBI population.
- These AEDS can potentially compromise the post - injury recovery.

Conclusions

- Newer AEDs need to be evaluated in the laboratory and large clinical trials, as these agents employ different pharmacological mechanisms for seizure control.
- The drugs that stop the process of epileptogenesis may be different from those that suppress seizures.

Epilepsy in the elderly

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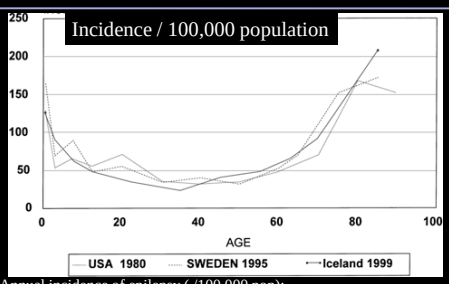
CONTENTS

- **Epidemiology:** the frequency of epilepsy is higher than generally acknowledged
- **Diagnosis:** How to exclude or confirm epilepsy
- **Etiology:** causes and risk factors
- **Treatment:** how to select and use antiepileptic drugs

EPIDEMIOLOGY



Annual incidence of epilepsy (/100,000 pop):
- All age groups: 80
- 65 to 69 yrs: 85.9
- > 80 yrs: 135

CAUSES AND RISK FACTORS

- **Onset of epilepsy:**
  - **Earlier in life: all types of epilepsy can be present in the elderly**
  - **Re-emergence of seizures in previously controlled patient with epilepsy**
  - **New onset epilepsy**

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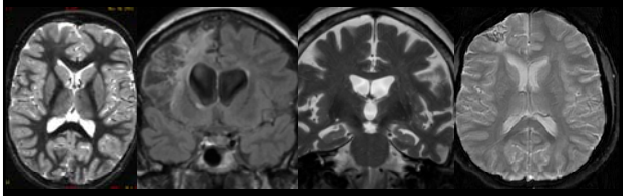
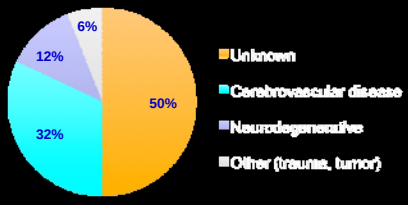
Causes of epilepsy (>64 yrs)





Hauser et al , 1992

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Cerebrovascular disease

- **Presentation:**
  - **Acute seizures (<48 hrs): no chronic treatment needed**
  - **10-13% develop seizures over 5 years**
  - **Seizure may be the first clinical manifestation (epilepsy is a predictor of subsequent stroke)**
- **Approach:**
  - **Complete stroke work-up in elderly with first sz**
  - **Include patients with unknown cause (normal brain MRI)**
  - **Consider secondary vascular prophylaxis in patients with first seizure**

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Neurodegenerative

- 10% patients with Alzheimer disease (x10 the incidence in a reference population)
- Can occur at any stage, or the first manifestation of the disease
- Treatment with antiepileptic drugs can increase cognitive decline

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Risk factors

- Depression >55 years: x6 risk of epilepsy [1]
- Hypertension: OR 1.57 [2]
- Sleep apnoea [3]

1. Hersdorffer et al, 2000
2. Ng et al, 2003
3. Chihorek et al, 2007

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DIAGNOSIS

- Detailed history, interview to witnesses
- Often referred for other conditions:
  - Altered mental status
  - Episodes of confusion or abnormal bahaviour
  - Memory lapses, transient global amnesia
  - Dementia
  - Sleep disorders
  - Syncope
- Differential diagnosis not always simple. Do not treat unless sure

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How accurate are seizure descriptions?

- 20 volunteers
  - 4 doctors working in a neurology ward
  - 10 medical students
  - 6 non-medical students
  - Viewed a video of a partial then secondary GTC Sz and gave a written account of 6 key features
- Results:
- Mean scores 3.5 (range 1-6)
- Unresponsiveness and lateralising features were often missed
- Left and right were often confused
- Highest scores by a medical and a non-medical student
- Lowest score by a doctor

Mannan and Wieshmann. Seizure 2003

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Electroencephalogram (EEG)

- Sharp waves in temporal regions are common in the elderly without epilepsy
- Clear epileptiform abnormalities present in 75% patients with epilepsy and 26% without epilepsy*
- Do not use EEG when history of syncope or other non-epileptic events is clear

*McBride et al, 2002

An EEG does not confirm or rule out epilepsy, it is one more piece of information and helps in the assessment of epilepsy type

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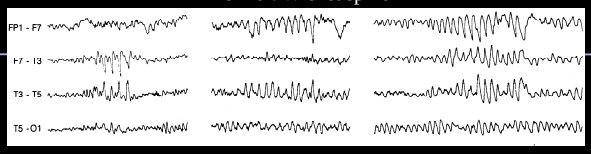
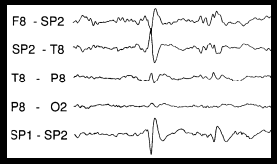
Normal: Wicket spike



Abnormal: epileptiform spike



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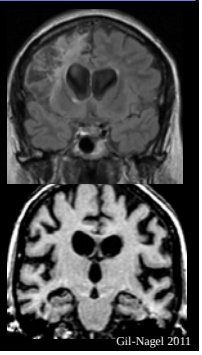
Brain MRI

- Common findings in the elderly:
  - Cerebrovascular disease: small vessel, silent stroke
  - Meningioma
  - Atrophy
- Does not necessarily indicate that the events under study are epileptic



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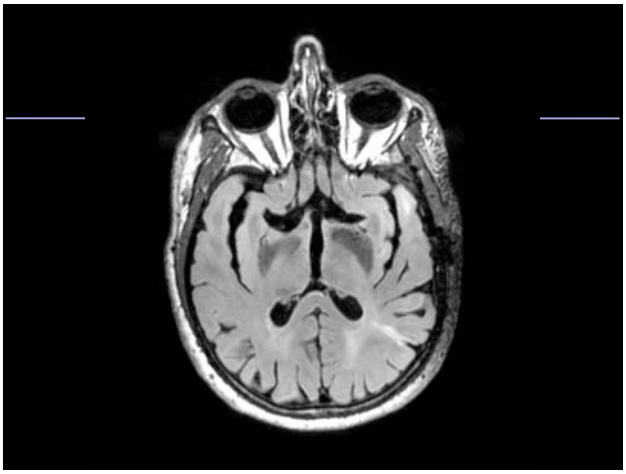
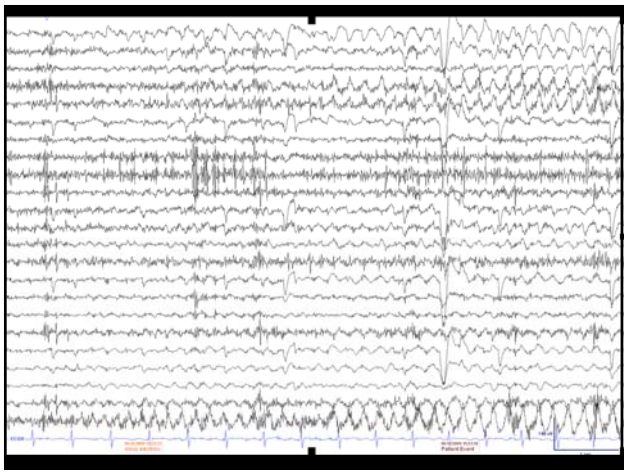
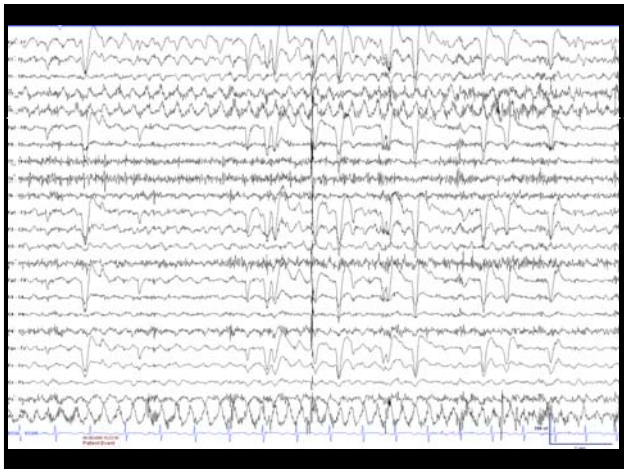
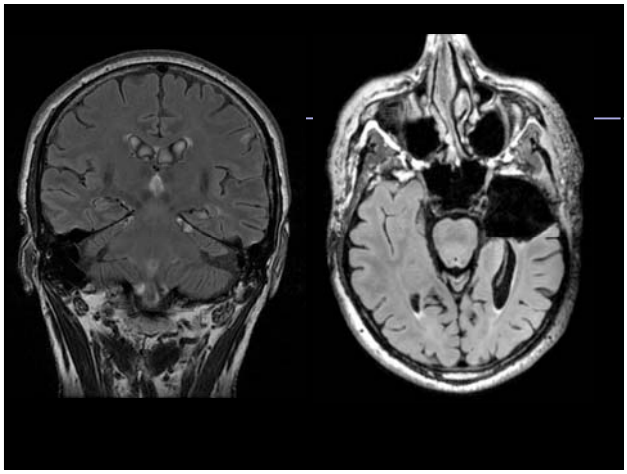
EPS

- 67 year old right handed male.
- Complicated febriles seizure at age 2
- Onset of GTC and CP seizures at 61
- Brain MRI: Left parietal silent stroke
- Treatment: CBZ, LTG, LEV, PHT. GTC controlled but not CP seizures
- Unable to work in his ca repair shop









Diferential diagnosis with syncope

- Asymptomatic arrhythmia, abnormalities on echocardiogram, positive tilt test. Not necessarily related to syncope
- If syncope is likely from clinical information consider multiple 24-48 Holter ECG or implantable recorder
- Clinical clues:
  - Prodrome
  - If clonic jerking, only 3 to 5 times
  - Recovering in the same spot, without confusion
  - First recovered hearing, then vision

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Video-EEG monitoring (telemetry)

- Prolonged EEG and video, duration 12 hours to 5 days
- Supervised environment to interact and provide appropriate treatment
- High yield, even when recurrence of episodes is low

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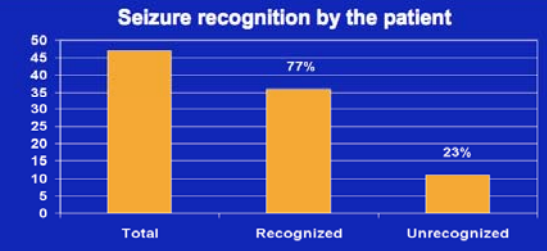
CFG

- 70 year old man
- Bizarre behaviour and confusion episodes, 3 times per week, since age 65
- Diagnosis: anxiety disorder.
- Normal interictal EEG

Ambulatory 24 hour EEG



502 patients
552 ambulatory 24 hour recordings
47 seizures

Tatum, 2001

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Self-Reported seizure rate does not correlate with time to first seizure during video-EEG

	Outpatient SZ Freq/Month	Days to First SZ
Low Frequency	**2.2**	**2.8**
Medium Frequency	**8.8**	**2.1**
High Frequency	**24**	**2.1**

Eisenman et al. Epilepsia. 2005 May;46(5):664-8

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TREATMENT

- **Higher rate of adverse events**
- **Comorbidities**
  - **Cognitive impairment**
  - **Bone loss**
  - **Hypertension, cerebrovascular disease**
  - **Thyroid disease, diabetes, dislipemia**
  - **… and more**
- **Polypharmacy**

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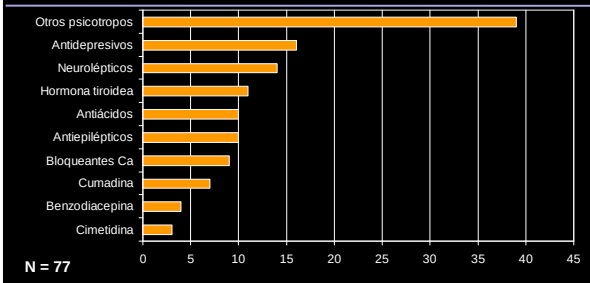
Polypharmacy in elderly with epilepsy



N = 77

Institucionalized elderly with epilepsy receives a mean of 5.6 drugs, compared to 4.6 for non-epileptic residents JC Cloyd, 94

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Drug-drug interactions

- Enzyme inducing Antiepileptic Drugs (AEDs)
  - Phenytoin
  - Carbamazepine
  - Phenobarbital
  - Primidone

→

- Decreased efficacy
  - Warfarin
  - Statins
  - Antidepresants
  - Antihypertensives
  - Antyarrhythmics
- Decreased vitamin D and sexual hormones

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Valproic acid induced CNS adverse effects

- Parkinsonism
- Weight gain
- Cognitive side effects
- Inhibition of clearance of other drugs
- Decreased vitamin D absorption

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Other adverse events with classic AEDs

- Drug induced or worsening of cardiac arrhythmia
  - Carbamazepine
  - Phenytoin
- Hyponatremia
  - Oxcarbazepine
  - Carbamazepine

  More common in patients in thiazide and other diuretics

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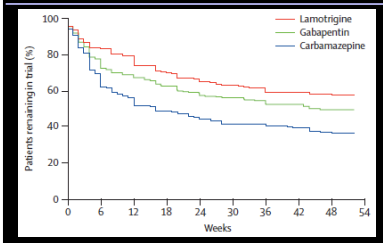
VA randomised controlled trial



New onset epilepsy
Age >65 yrs

Doses:
-LTG 50 mg bid
-GBP 300 mg tid
-CBZ 200 mg bid

Lamotrigine versus carbamazepine p< 0.00001
Gabapentin versus carbamazepine p<0.008

Rowan et al, 2005

Differences related to tolerability not efficacy

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Open studies

- Gabapentine
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Topiramate

Overall there is a trend to avoid older AEDs

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Initiation of treatment

- Start treatment:
  - Diagnosis is certain
  - After two seizures

    or
  - One seizure if:
    - Severe event
    - Lesion in MRI
    - Abnormal EEG
    - Driving needs

Higher rate of recurrence of seizures after first episode in the elderly*

*Musicco et al 1997

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Drug use

- Only mild differences in efficacy
- Select AED based on side effect profile
- Higher rate of idiosyncratic skin reactions in elderly (avoid those with higher risk if previous history of allergy)
- Start always low dose and increase slow
- If not well tolerated lower dose and consider changing to another AED
- If not effective increase dose or change to other with different mechanism of action

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Drug selection

- **Levetiracetam:**

increments of 250 mg/day each week or two up to 500 mg twice daily

- **Lamotrigine:**

increment of 25 mg/day each 2 weeks to 50 mg twice daily

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	Advantages	Disadvantages
Lamotrigine	Good tolerability Studied in elderly	Slow titration Skin rash Insomnia
Levetiracetam	Fast titration Lack of interactions	Sedation Behavioural problems
Gabapentin	Lack of interactions Studied in elderly	Low efficacy Three times/day dosing
Topiramate	Weight loss in obesity	Cognitive impairment Renal stones
Oxcarbazepine	Efficacy in focal epilepsy	Drug interactions Hyponatremia Skin rash
Pregabalin	No interactions	Weight gain Few data in elderly
Zonisamide	Once daily No interactions	Sedation Skin rash Renal stones Few data in elderly
Carbamazepine	Cheap Studied in elderly	Drug interactions Skin rash Osteoporosis Hyponatremia
Valproic acid	Cheap Efficacy in myoclonic and absence seizures	Drug interactions Parkinsonism Osteoporosis Weight gain

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CONCLUSIONS

- Consider epilepsy in all patients with transient impairment of neurological function
- Maximize diagnostic efforts
- Consider treatment even after first seizure when diagnosis is clear
- Select a drug, start low, increase slow and monitor for adverse events

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AG

- 76 yo male
- Onset of multiple (100's) of episodes per day (sleep and awake):
  - Alternating tonic contraction of one arm and face (mouth opening), independent, bilateral.
  - Facial muscle contractions
  - Myoclonus, tics
- Normal interictal and ictal EEG, CT scan, and CSF
- Resistant to CBZ, LTG, GBP, VPA
- Resolution after 6 months

Faciobrachial Dystonic Seizures Precede Lgi1 Antibody Limbic Encephalitis

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- 29 Patients, adults
- Distinctive brief dystonic szs involving arm and ipsilateral face
- 26 developed limbic encephalitis after this
- All positive to Ab anti-VGKC, 89% antigen specific to Lgi1
- Initial phase: Normal brain MRI, 7 with ictal epileptiform activity on EEG
- Limbic encephalitis phase (amnesia and confusion): hyponatremia, bilateral mesial temporal lesions, altered metabolism in basal ganglia
- AEDs ineffective, often severe allergic reactions.
- Immune therapy often very effective