4° CORSO RESIDENZIALE
EEG e POTENZIALI EVOCATI
22 – 27 NOVEMBRE 2021

Encefalopatie epilettiche "precoci"

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Outlines

- Definitions
- What is not EE and why
- What certainly is EE
- Different etiologies same evolution toward EE
- How affects the brain
- New classification

Epileptic encephalopathy - Definitions

- "Condition in which the epileptiform abnormalities are believed to contribute to progressive disturbance in cerebral function."

  (Engel, 2001)

- "Evidence suggests or supports the notion that there is an epilepsy-dependent neurodevelopmental or neurodegenerative process involved in the evolution of the syndrome (as opposed to an underlying metabolic, degenerative, or encephalitic process),"

  (Engel, 2006)

- Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time.
- These impairments may be global or more selective and they may occur along a spectrum of severity.
- Although certain syndromes are often referred to as epileptic encephalopathies, the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy.

  (Berg et al., 2010)

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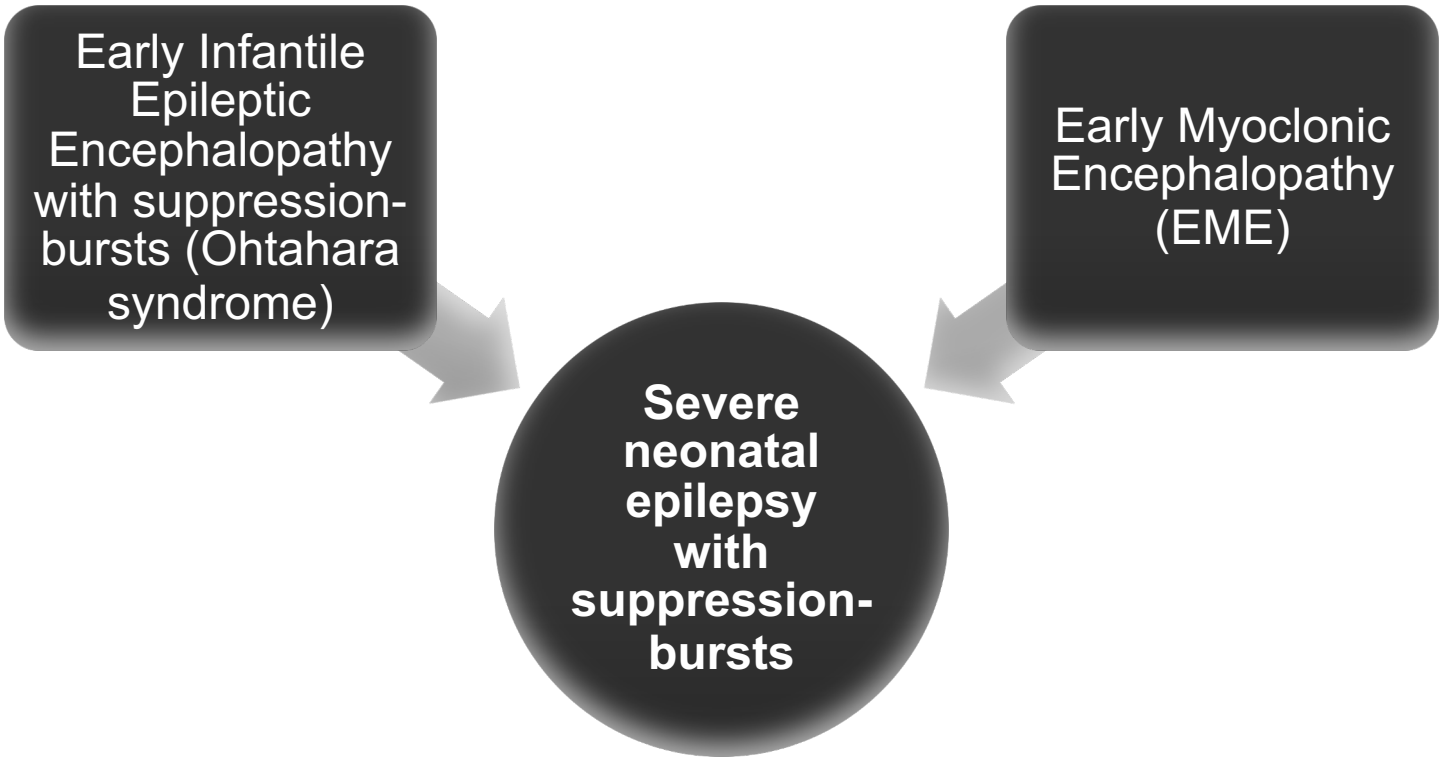
ROADMAP….. 2017

Epileptic encephalopathies

- Early myoclonic encephalopathy
- Ohtahara syndrome
- West syndrome
- Dravet syndrome (Dravet-like syndromes)
- Myoclonic status in non-progressive encephalopathies
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome
- Epilepsy with continuous spike-waves during slow-wave sleep

Berg et al., 2010


Early Infantile Epileptic Encephalopathy with suppression-bursts (Ohtahara syndrome)
Early Myoclonic Encephalopathy (EME)
Severe neonatal epilepsy with suppression-bursts

Early Onset Epileptic Encephalopathies (EOEE)

- In the neonate:
  - Clinically preservation of sleep-wake cycle
  - Abnormale posturing and movements (hypotonia o hypertonus)
  - Several type of EEG suppression-bursts, both during wakefulness and sleep
  - Multifarious seizures:
    - Epileptic spasm
    - Myoclonus
    - Focal seizures (motor, autonomic, head eye deviation)
    - Seizures with bilateral motor involvement

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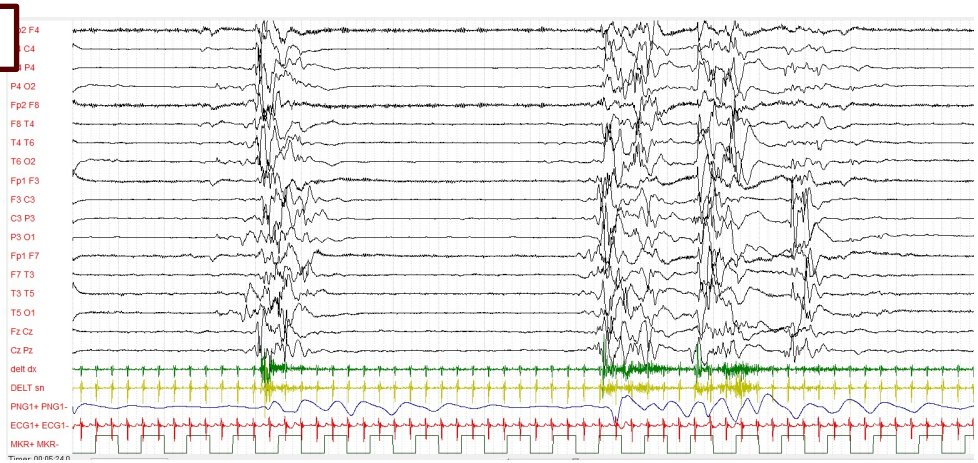
Epileptic encephalopathy or encephalopathy with epilepsy?

- Neonatal onset of epileptic seizures
- EEG pattern: burst suppression
- No response to AED
- Absence of acquisition
- No eye contact

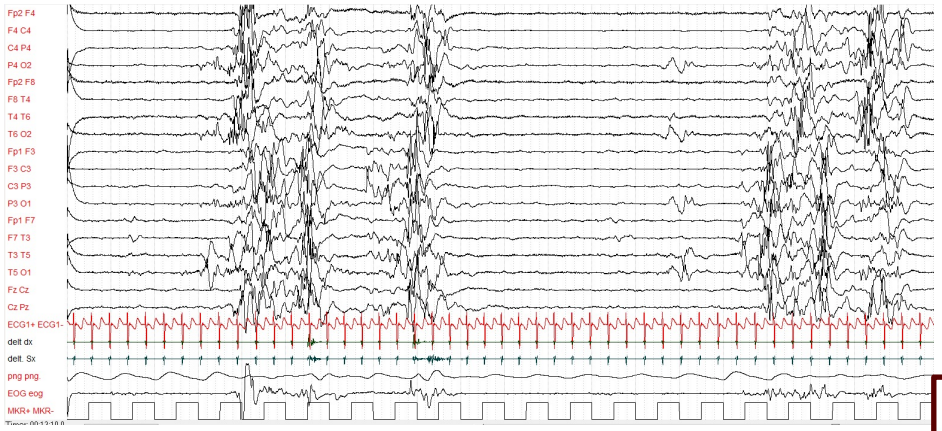
- Mutation STXBP1:
- Persistence of the EEG pattern
- Persistence of seizures
- No acquisitions

Dd 60 days

awake



sleep



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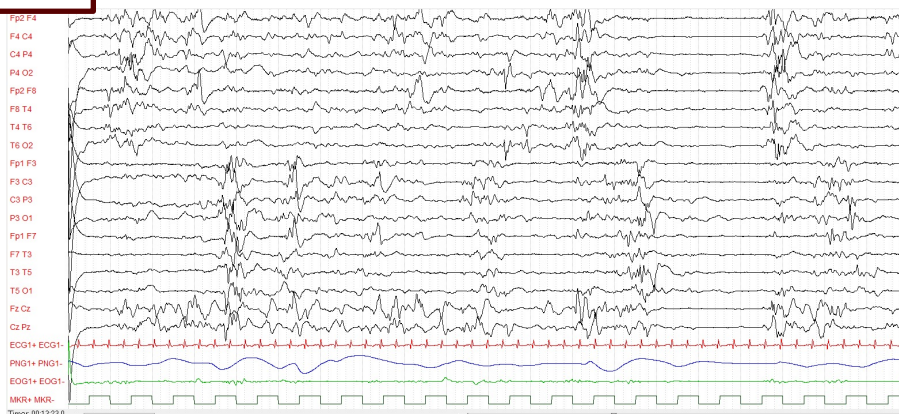
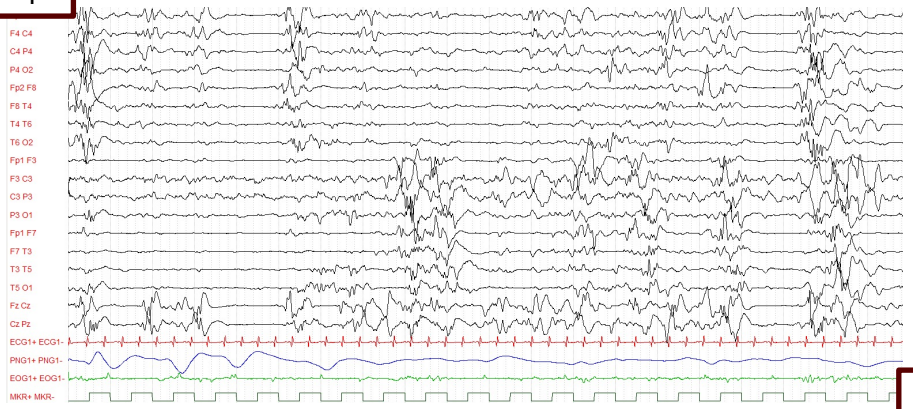
ZC 65 days

awake



sleep



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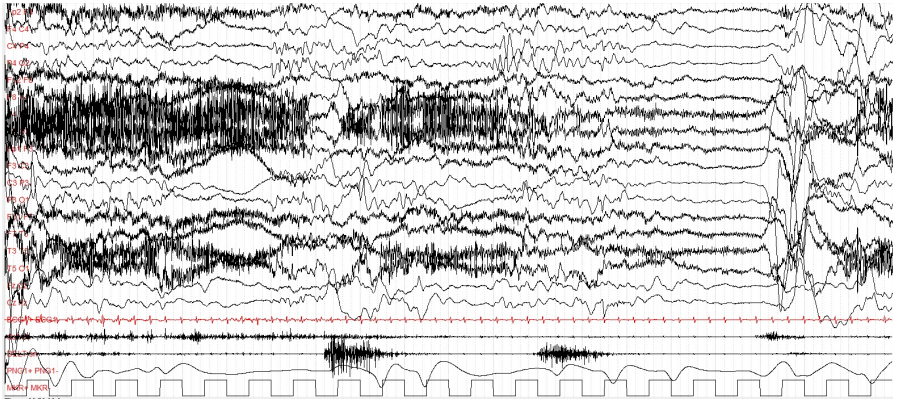
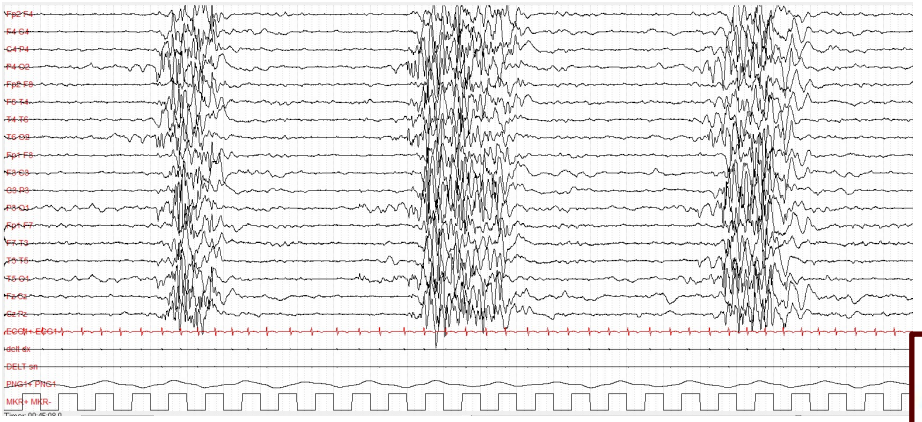
awake



sleep



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Ohtahara Syndrome
Early Myoclonic Encephalopathy (EME)

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- Etiology is variable: brain malformations, inborn error of metabolism, genetic abnormalities….
- Onset is so early that it is not possible to determine if the associated severe cognitive and behavioral impairments are due to either seizures and epileptic abnormalities or to genetic, structural or metabolic brain abnormalities.
- The possibilities of clinical improvement are scarce.

Epileptic Encephalopathies

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- Which factors play a key role in triggering the evolution towards an epileptic encephalopathy? Is all determined by genetic mutations or is might be an association of effects?

- What pathogenetic mechanisms take place during this evolution? How epileptic activity interferes with cognitive networks?

West syndrome
Lennox-Gastaut syndrome
Epilepsy with continuous spike-waves during slow-wave sleep (CSWS)

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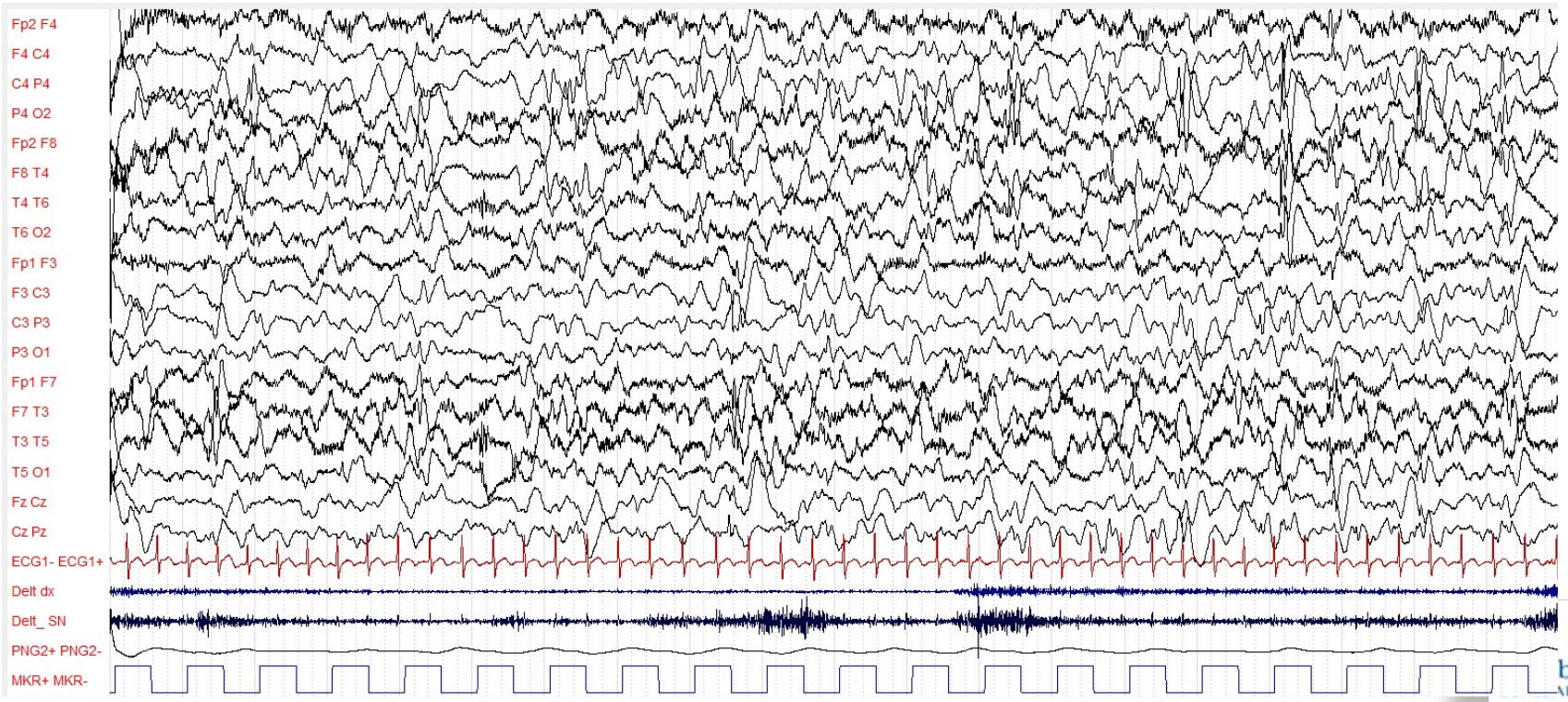
- Etiologies are variable.
- Peculiar evolution of epilepsy towards a syndrome specific electro-clinical picture.
- Quantifiable cognitive and motor regression, characterized by an evident worsening of the neuropsychological profile when compared to pre-onset neurodevelopmental phenotype.
- Variable evolution, ranging from complete remission to very severe conditions, such as drug resistant epilepsy and severe mental retardation.

West Syndrome

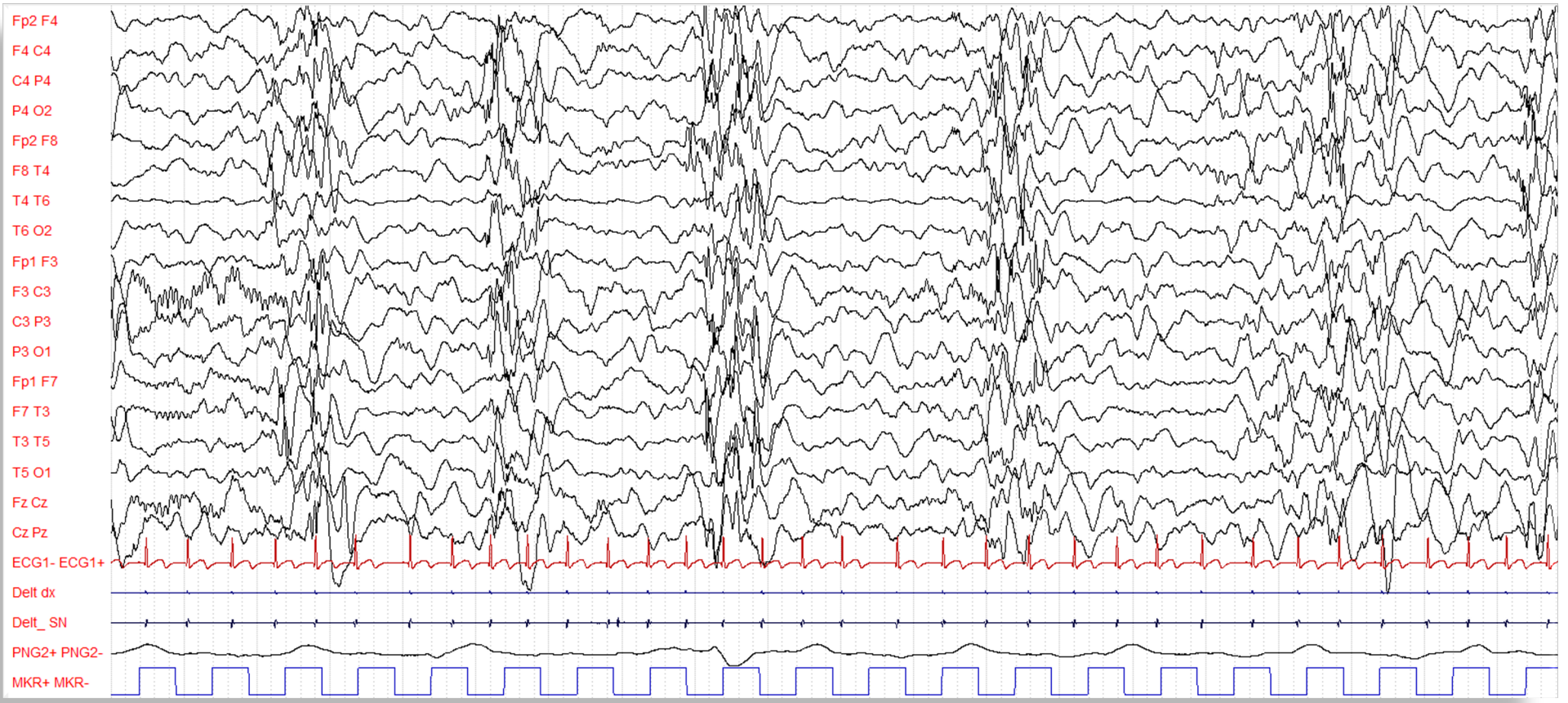
Severe epileptic encephalopathy characterized by:

- epileptic spasms
- hypsarrhythmic EEG pattern
- developmental delay

Interictal: Hypsarhyitmya



During sleep: alternating paroxysmal pattern



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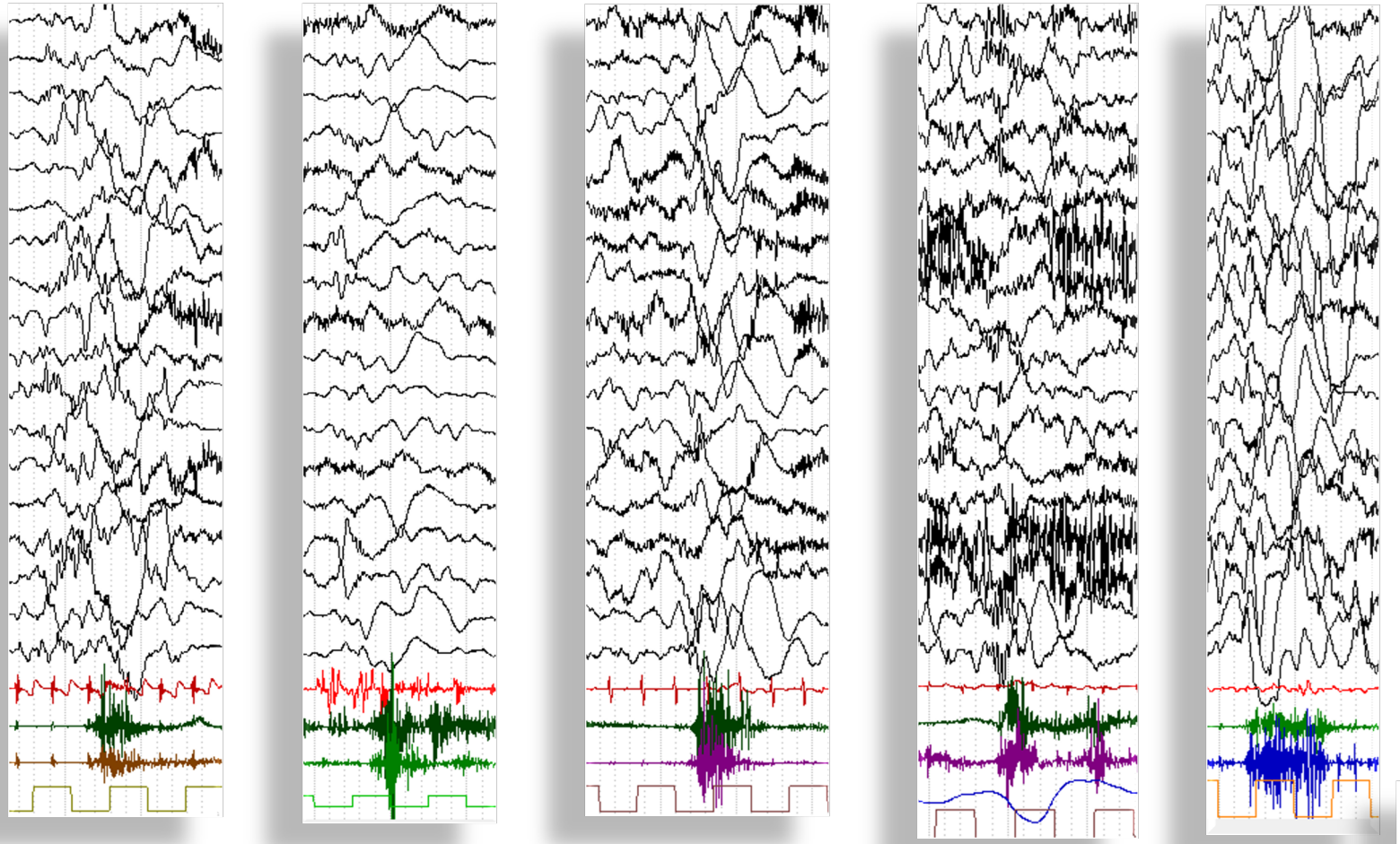

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Epileptic Spasms

- Severe type of epileptic seizure
- Often drug resistant
- Preceded or followed by focal seizures
- Frequently associated with an epileptic encephalopathy
- Children with focal, hemispheric or diffuse cerebral lesions
- No obvious cerebral lesion can be found and psychomotor development might be normal until the onset of the spasms
- Genetic epilepsies

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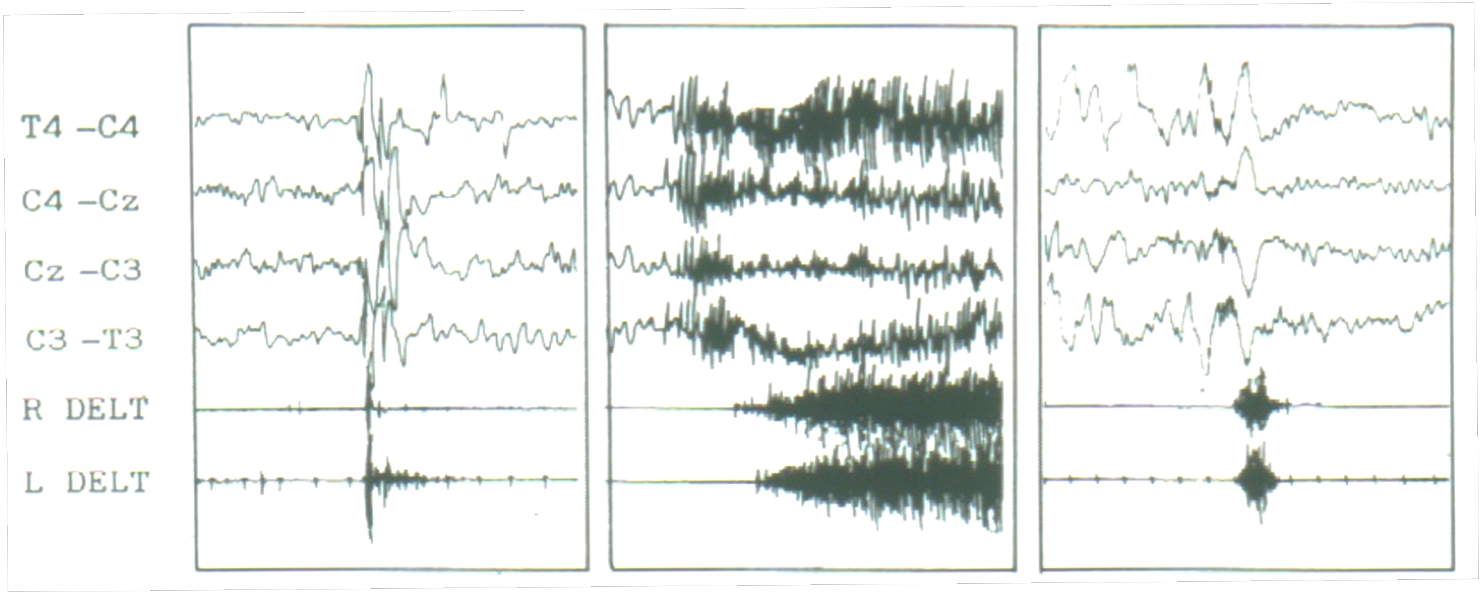
Epileptic spasm - definition



Myoclonic seizure **Tonic seizure** **Epileptic spasm**

Fusco and Vigevano, Epilepsia 1993

- ✓ A sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not as sustained as a tonic seizure.
- ✓ Limited forms may occur: grimacing, head nodding, or subtle eye movements.
- ✓ Epileptic spasms frequently occur in clusters.
- ✓ Infantile spasms are the best known form, but spasms can occur at all ages. They commonly occur in clusters and most often during infancy.

Fischer et al., Epilepsia 2017

Epileptic spasm - definition

Instruction manual for the ILAE 2017 operational classification of seizure types

[1]Robert S. Fisher, [2]J. Helen Cross, [3]Carol D'Souza, [4]Jacqueline A. French, [5]Sheryl R. Haut, [6]Norimichi Higurashi, [7]Edouard Hirsch, [8]Floor E. Jansen, [9]Lieven Lagae, [10]Solomon L. Moshé, [11]Jukka Peltola, [12]Eliane Roulet Perez, [13]Ingrid E. Scheffer, [14]Andreas Schulze-Bonhage, [15]Ernest Somerville, [16]Michael Sperling, [17]Elza Márcia Yacubian, and [18,19]Sameer M. Zuberi on behalf of the ILAE Commission for Classification and Terminology

Epilepsia, **(*):1–12, 2017
doi: 10.1111/epi.13671

- Epileptic spasms may require **detailed video-EEG monitoring** to clarify the nature of onset, but doing so is important because a focal onset may correspond to a treatable focal pathology.

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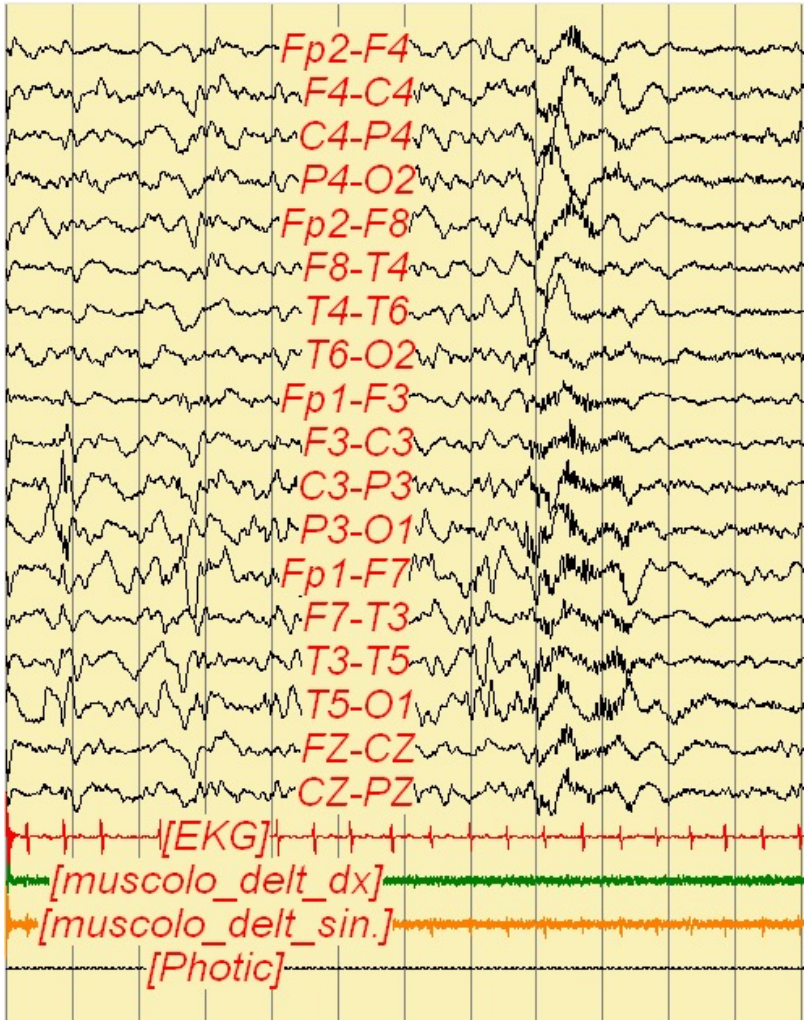
Definition

Epileptic spasms, other than a peculiar distinct seizure type, belong to *many different syndromic entity*, of which West syndrome is only the most well known

ICTAL EEG PATTERNS

- SLOW WAVE
- FAST ACTIVITY
- ATTENUATION



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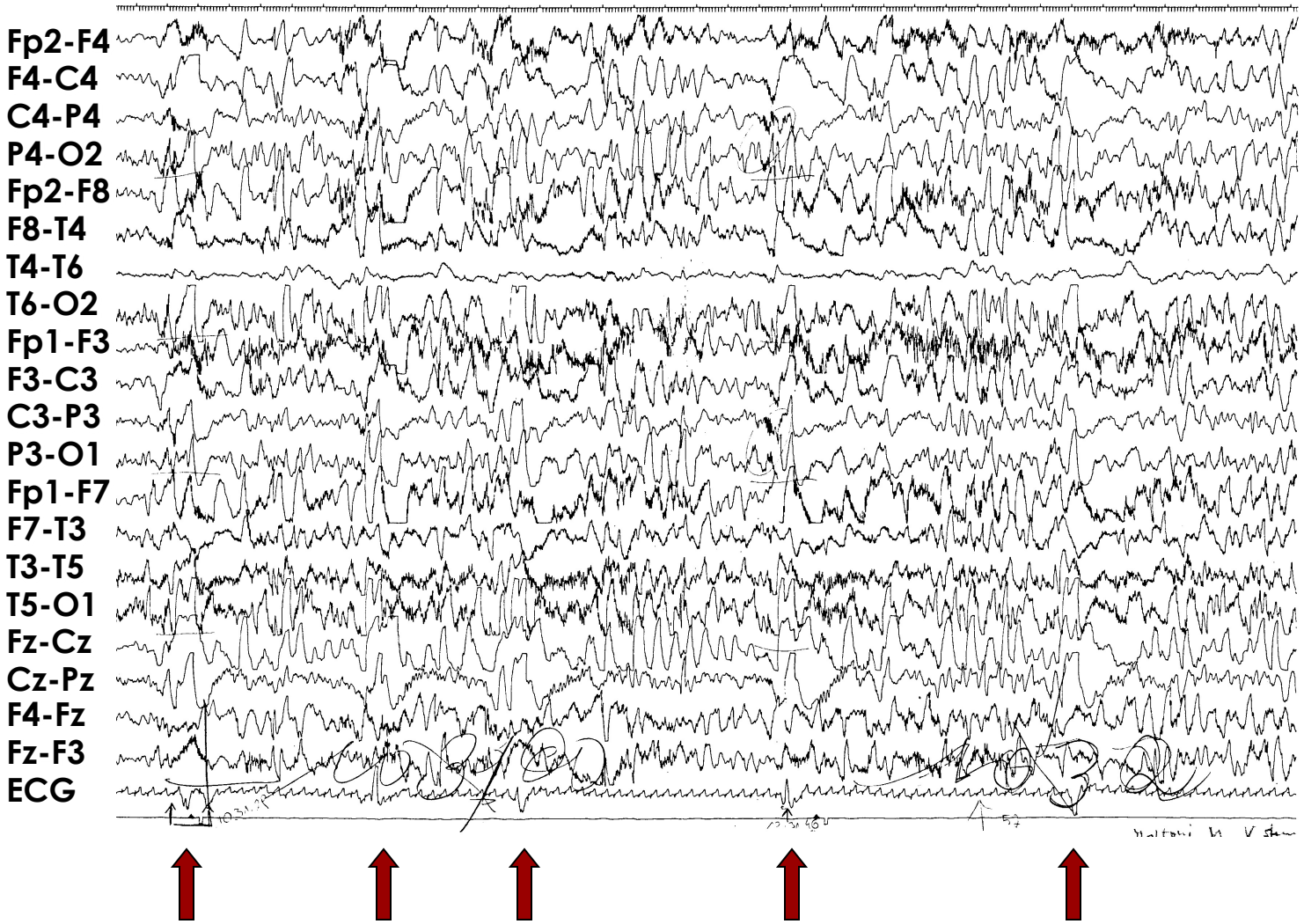
Mol.Mar. 11 m, Non-lesional Infantile Spasms



A

B

Vigevano F, Specchio N et al. 2007

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Cluster of spasm as a single ictal event (?)

- Spasms usually occur in cluster, mainly on awakening
- Is the cluster a single prolonged ictal event?

Pal.Tom. 9m, Left Temporal EEG abnormalities, normal MR

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Phenomena reported to occur in association with ictal events in infantile spasms

- Ocular events
  - Eye deviation
  - Nystagmoid motion
  - Eye opening or closing
  - Pupillary dilatation
  - Lacrimation
- Respiratory rate alteration
- Hiccups
- Crying
  - After seizure
  - During seizure
- Laughter
- Grunting noise
  - Smile
  - Grimace
- Tongue/mouth movements
- Autonomic alterations
  - Heart rate changes
  - Pallor
  - Cyanosis
  - Sweating
  - Flushing
- Decreased responsiveness
- Focal seizures

Frost and Hrachovy, 2003

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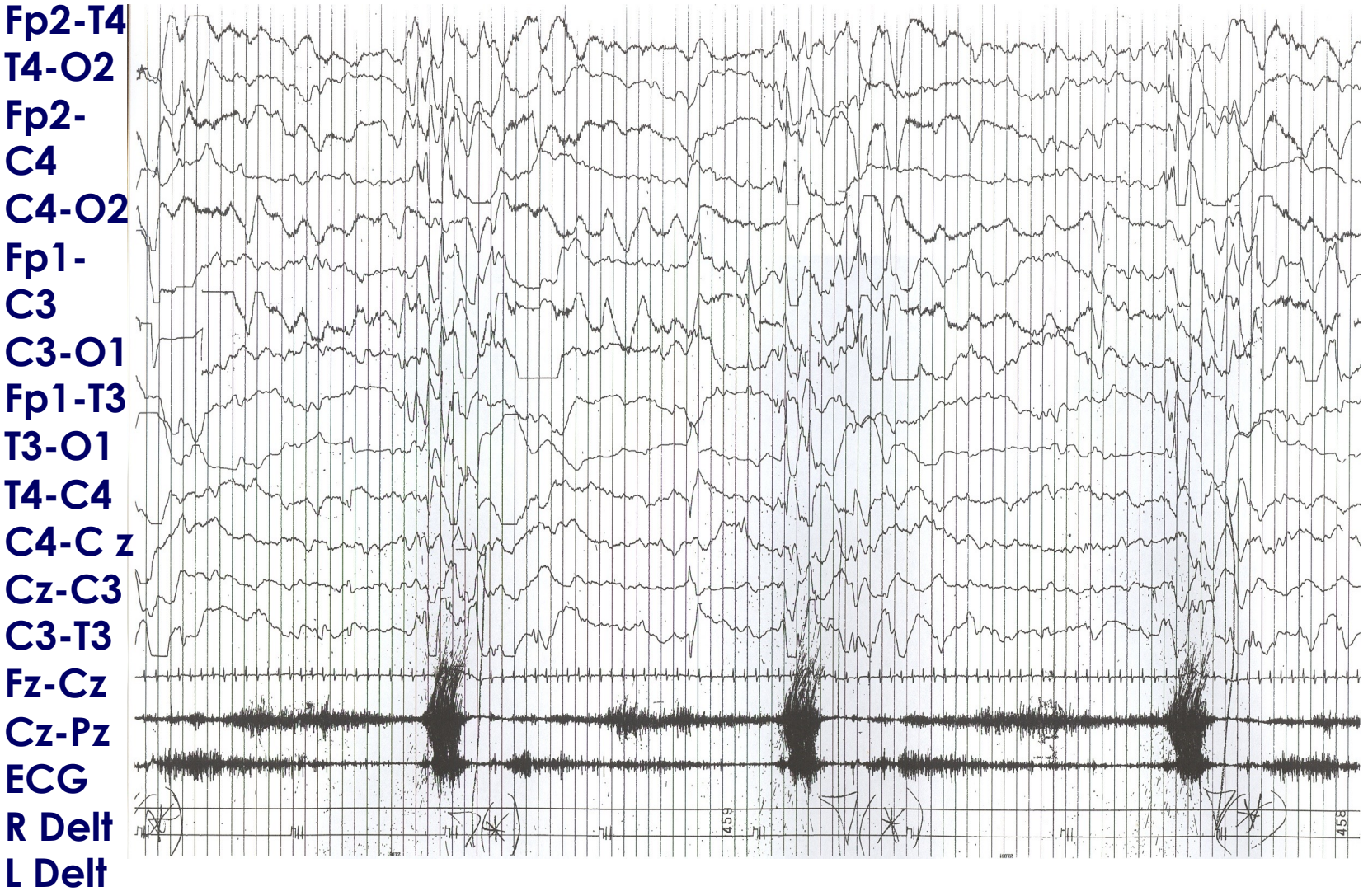
Bet.Hag. 6m, left frontal cortical dysplasia



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SUBTLE SPASMS

- Isolated signs of spasms
- Beginning of a cluster of spasms
- If we observe a cluster of spasms we see that there are some ictal events in which the movement of the limbs and trunk is very slight or almost absent and the ictal signs are limited to yawning, gasping, facial grimacing and staring
- These minimal clinical events are called "subtle spasms"

Lux and Osborne, 2004

Coi.Chi. 7m, crytpogenic etiology, normal MR

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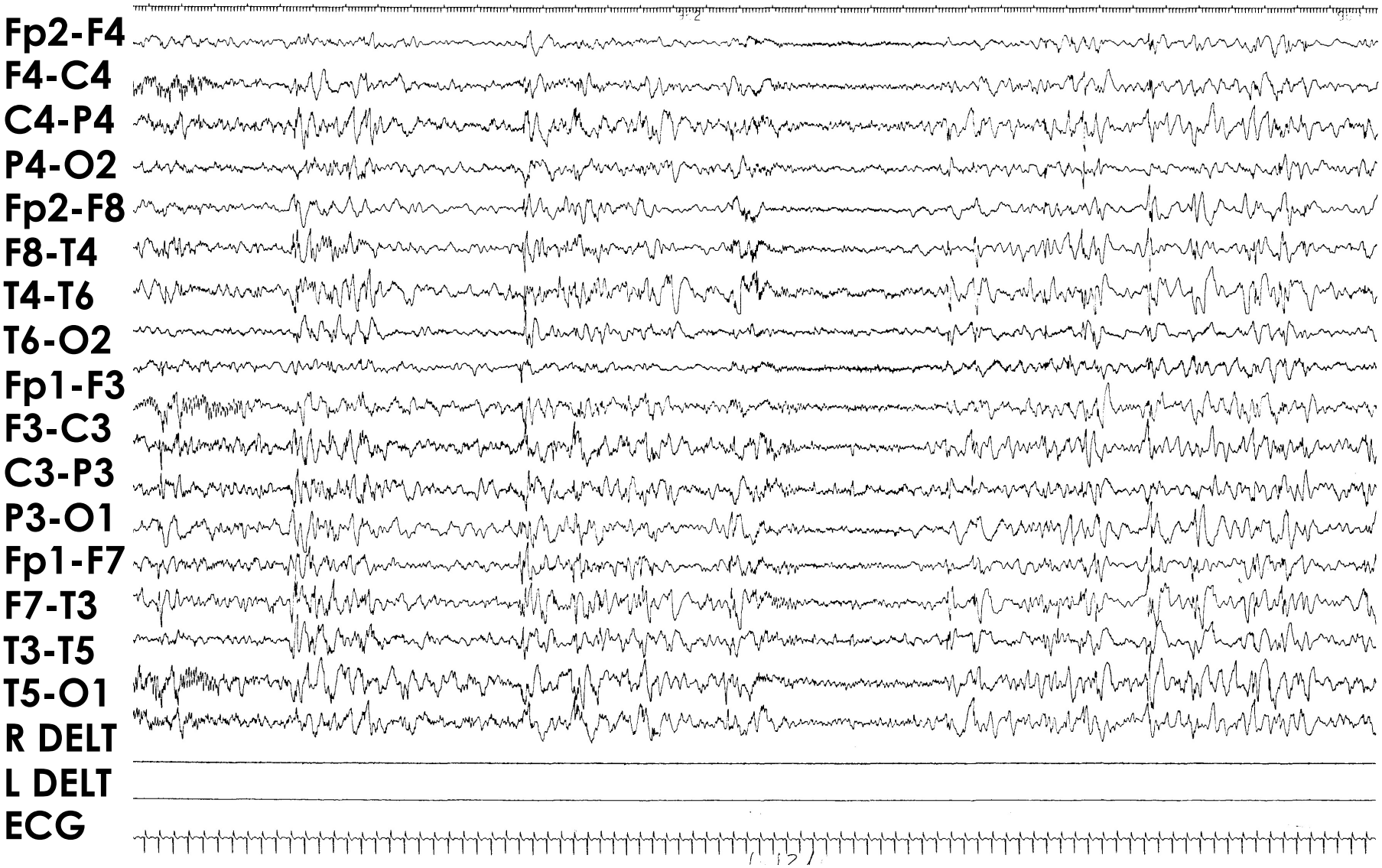

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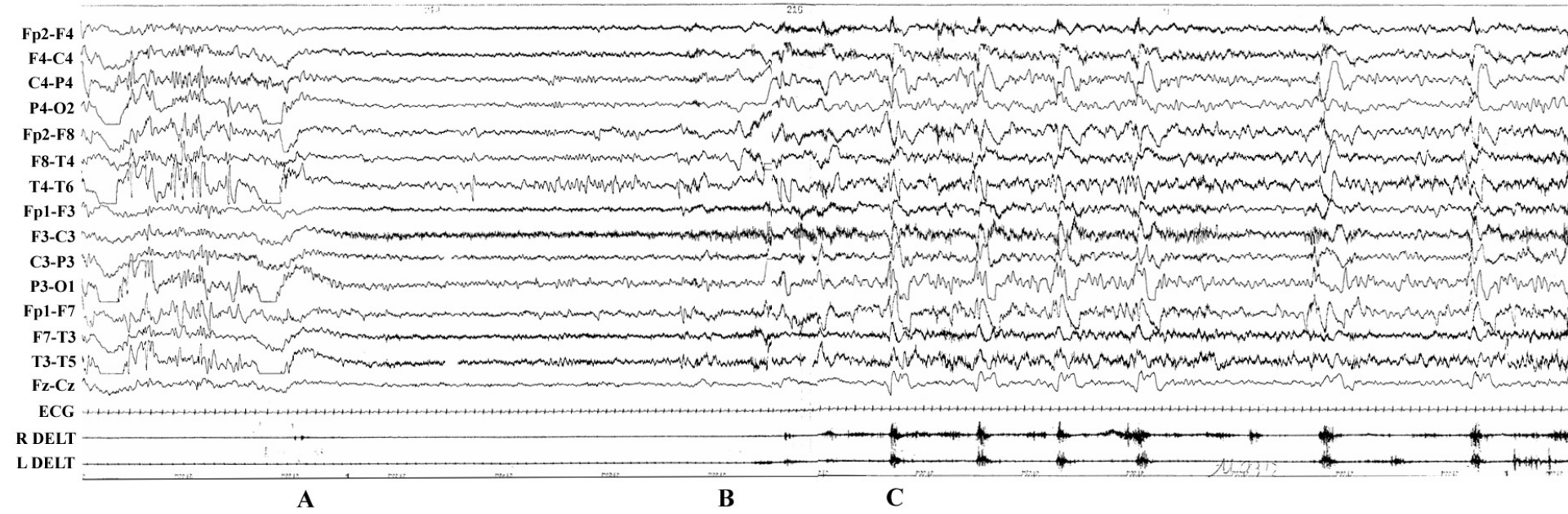
Occurrence of epileptic spasms and partial seizures in close temporal association (cortical trigger?)

- three different pattern of association between epileptic spasms and focal seizures:

  - the cluster follow or start or precede the partial event

- only the pattern of focal seizure constantly followed by a cluster of spasms clarify the role of the cortex in facilitating the epileptic spasms through descending electrical volley to the brainstem

Pachatz et al. (2003)



Vigevano F, Specchio N et al., 2007

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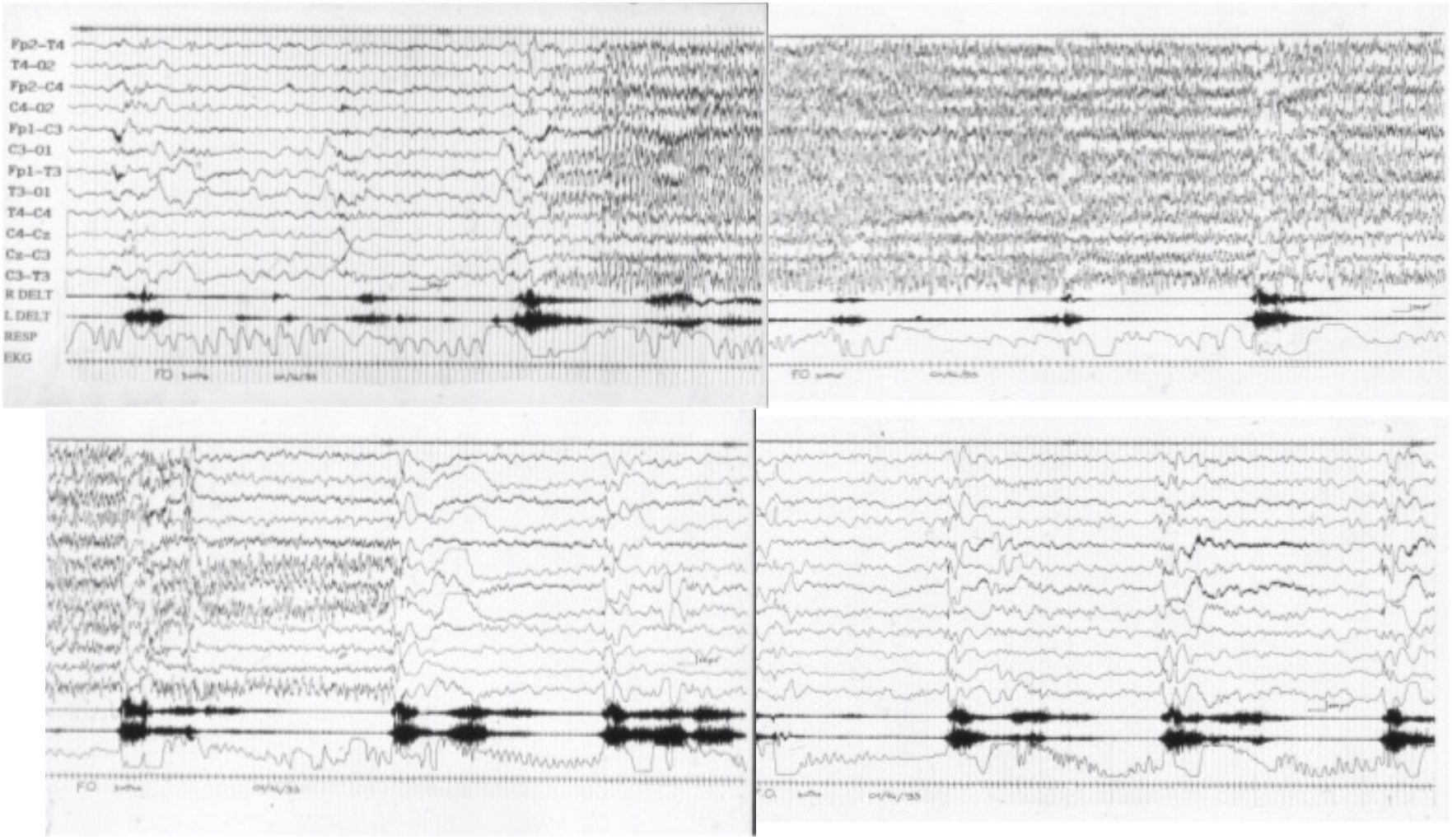
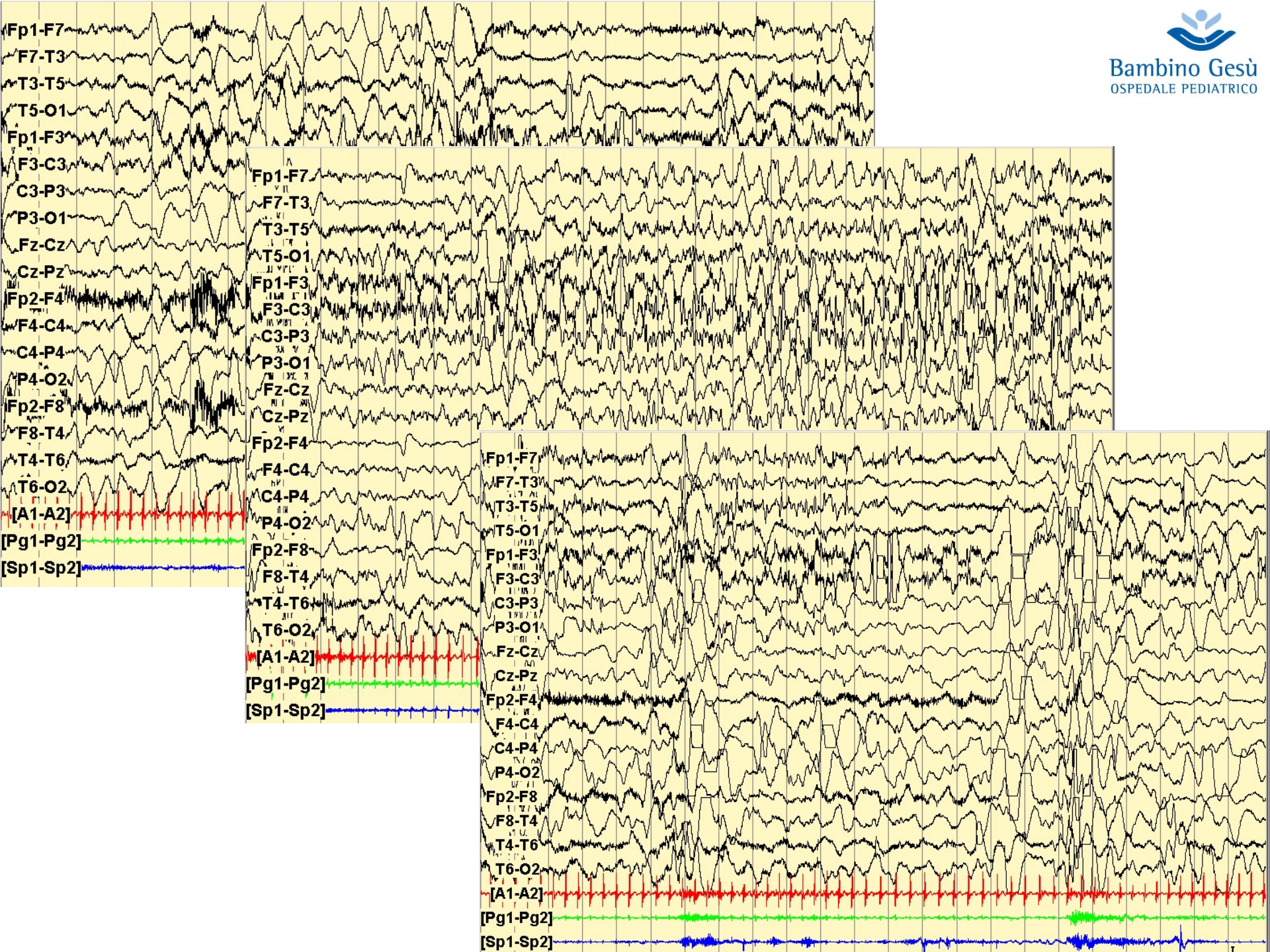
O.F. 3 m – Left frontal focal cortical dysplasia





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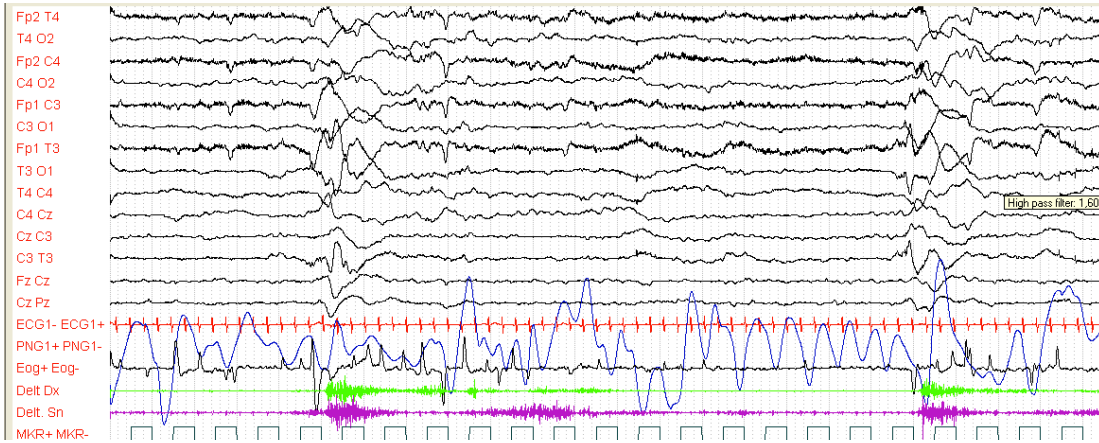

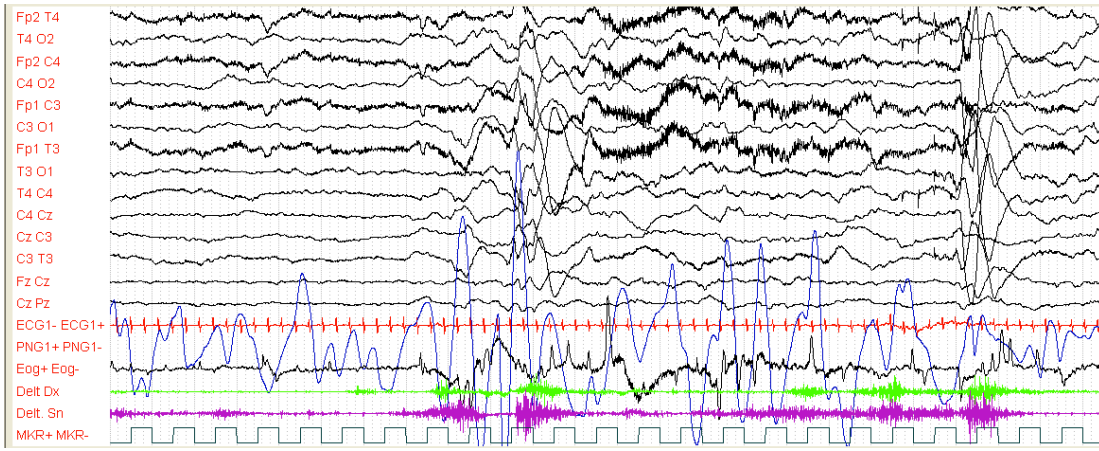

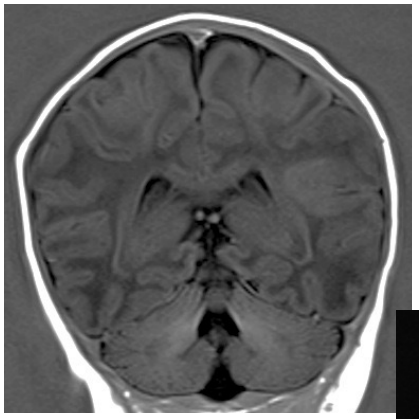

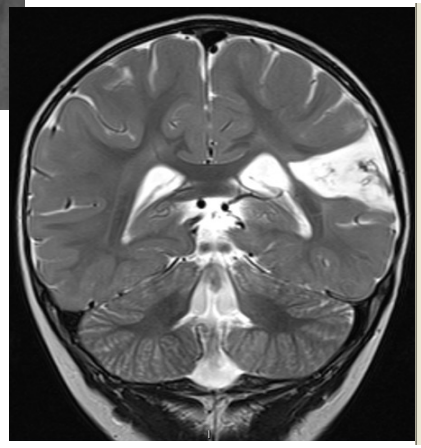

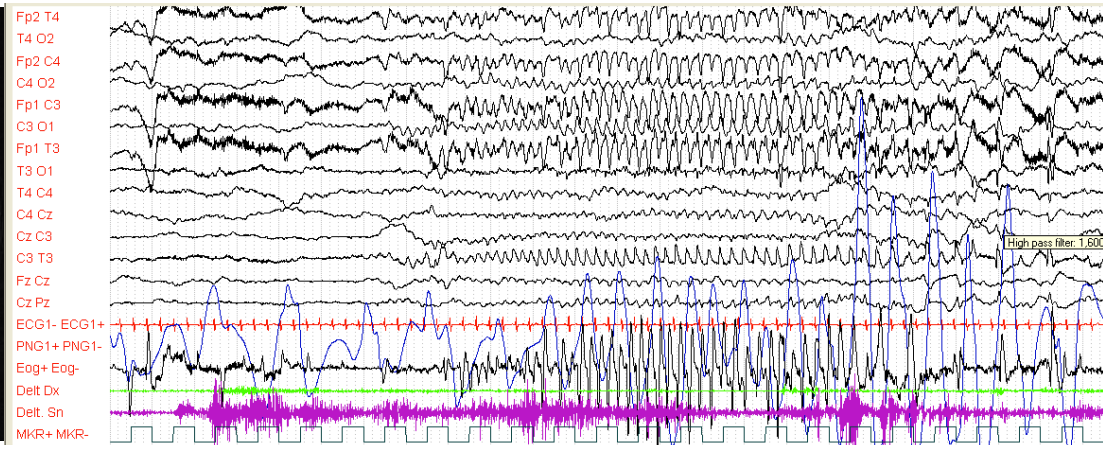

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Migrating Partial Seizures in Infancy

CLINICAL PRESENTATION

- Many of the motor manifestations are relatively subtle
- Electrical seizures
- Autonomic signs (flushing of the face, salivation, and apnea)
- Seizures are relatively brief but tend to recur in series of 5-30 seizures
- Clusters may last up to 5 days, at times requiring intenisve care
- Initial seizures are rare (once a week)

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Migrating Partial Seizures in Infancy

CLINICAL PRESENTATION

- Progressive neurological deterioration
- Major axial and limb hypotonia
- Loss of visual contact
- Inability to grasp
- Complete loss of other motor and social skills
- Acquired microcephaly

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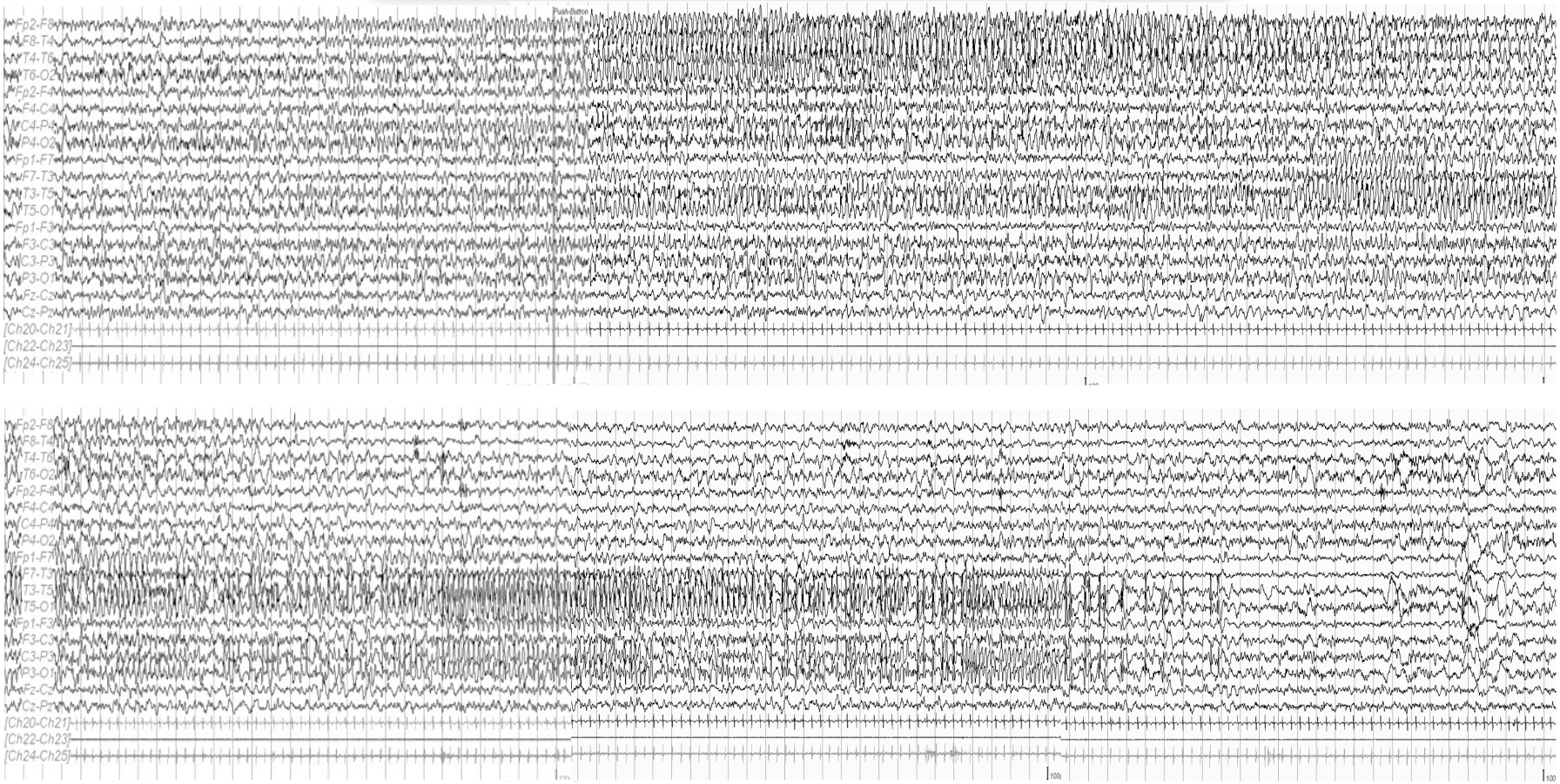
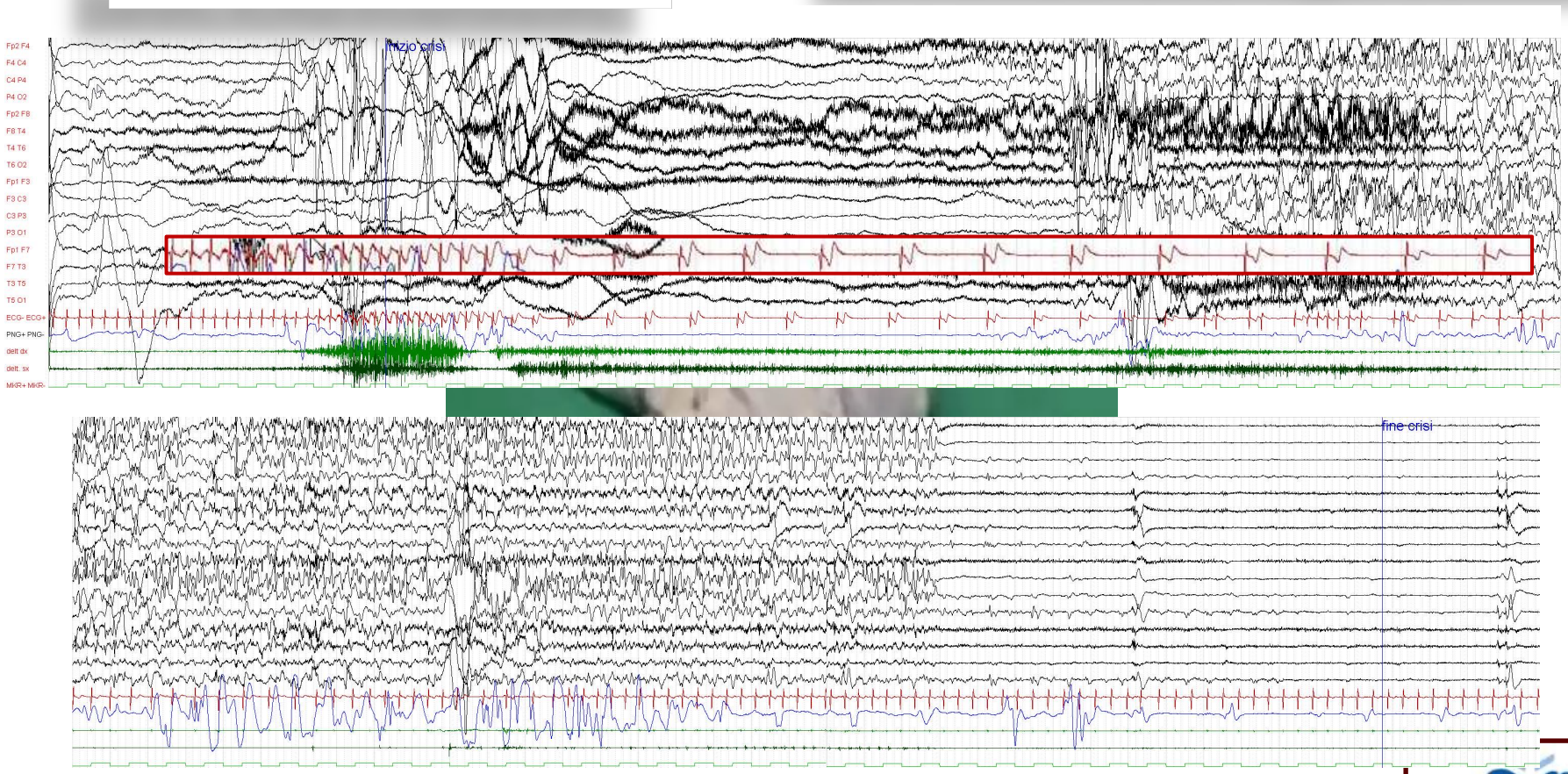
MPSI - Mir.Lat., 4 months, focal seizure, minimal signs



Genetic, KCNQ2 Encephalopathy

Type of clinical/EEG pattern suggestive of……



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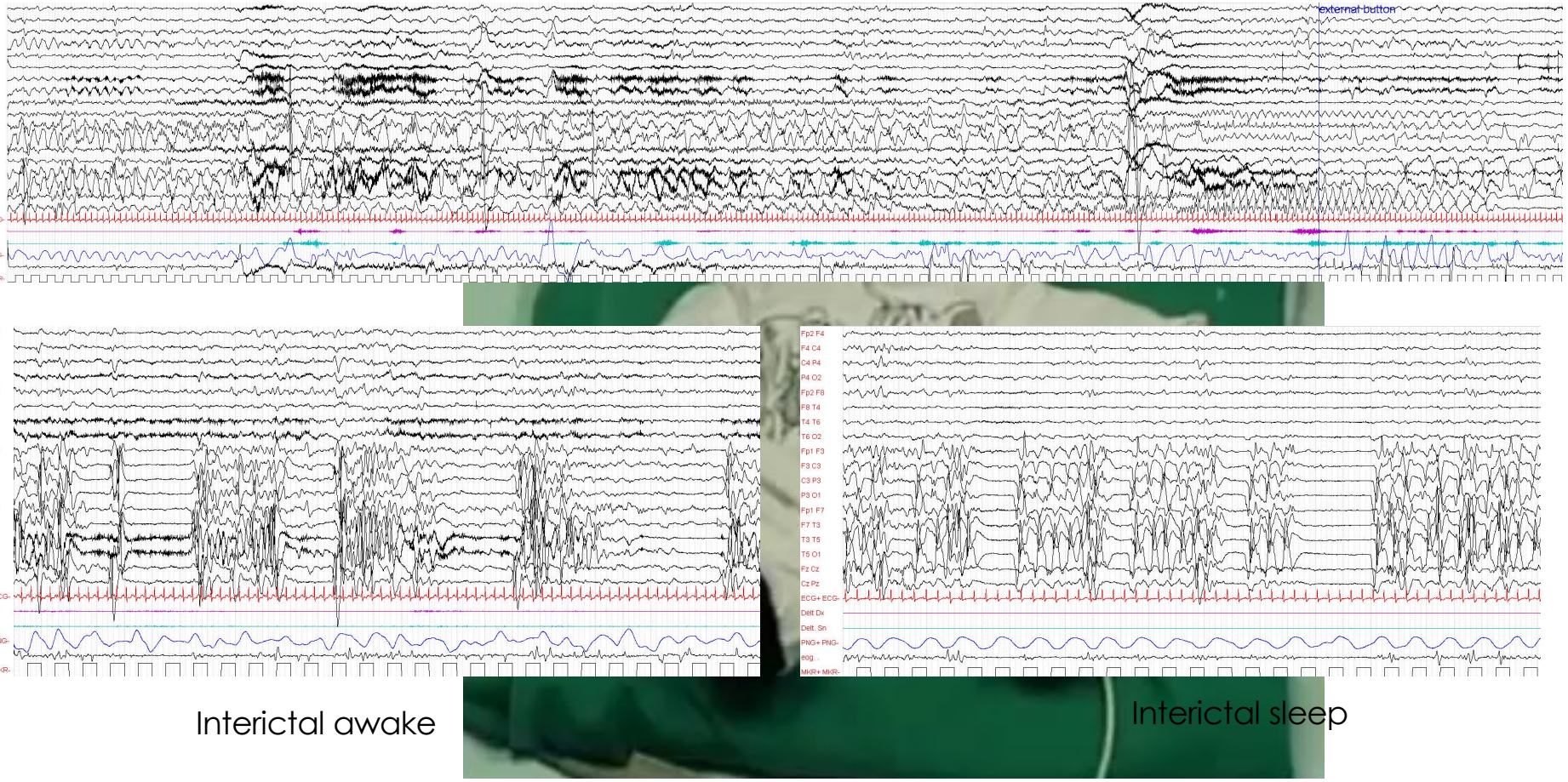
Type of clinical/EEG pattern suggestive of…….

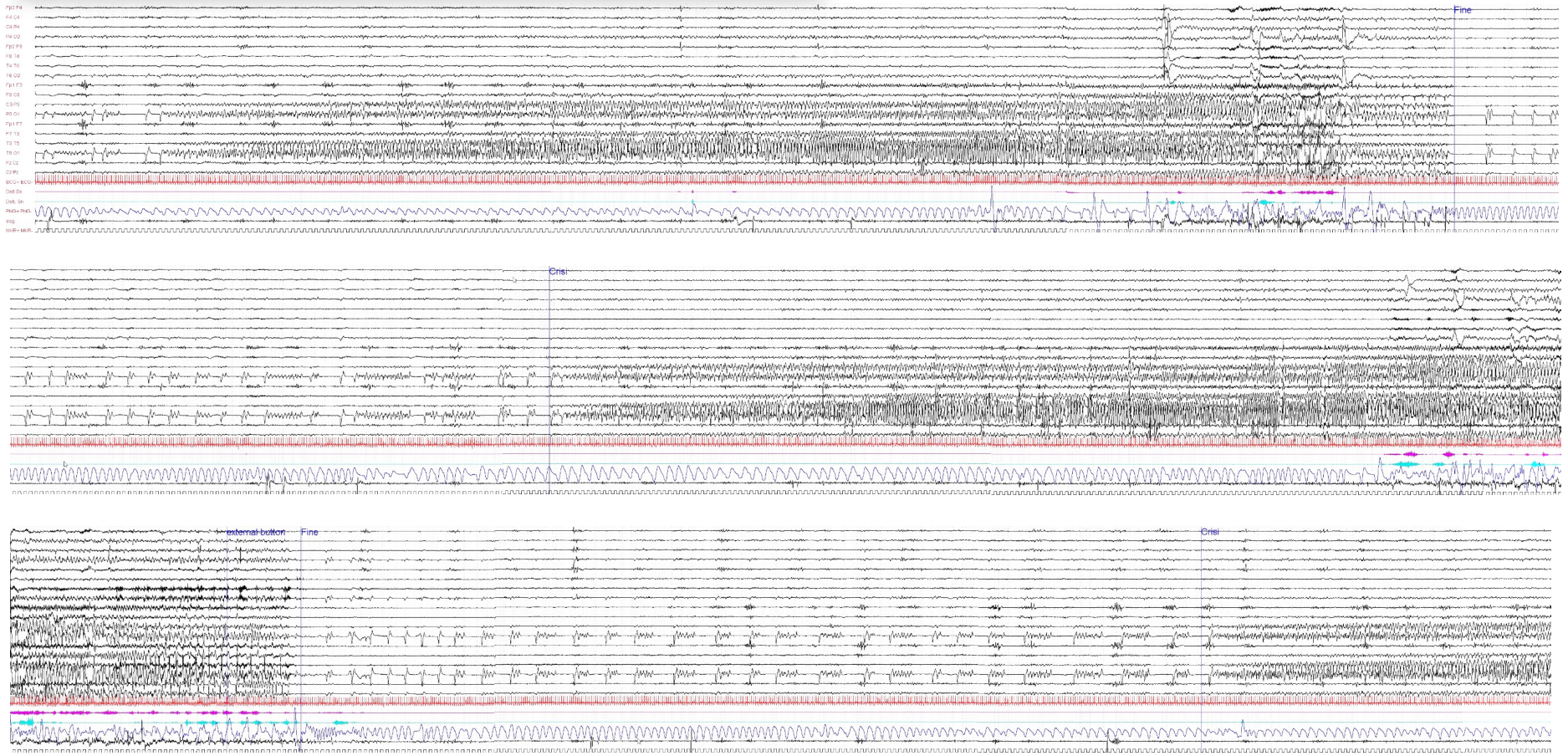


Interictal awake

Interictal sleep

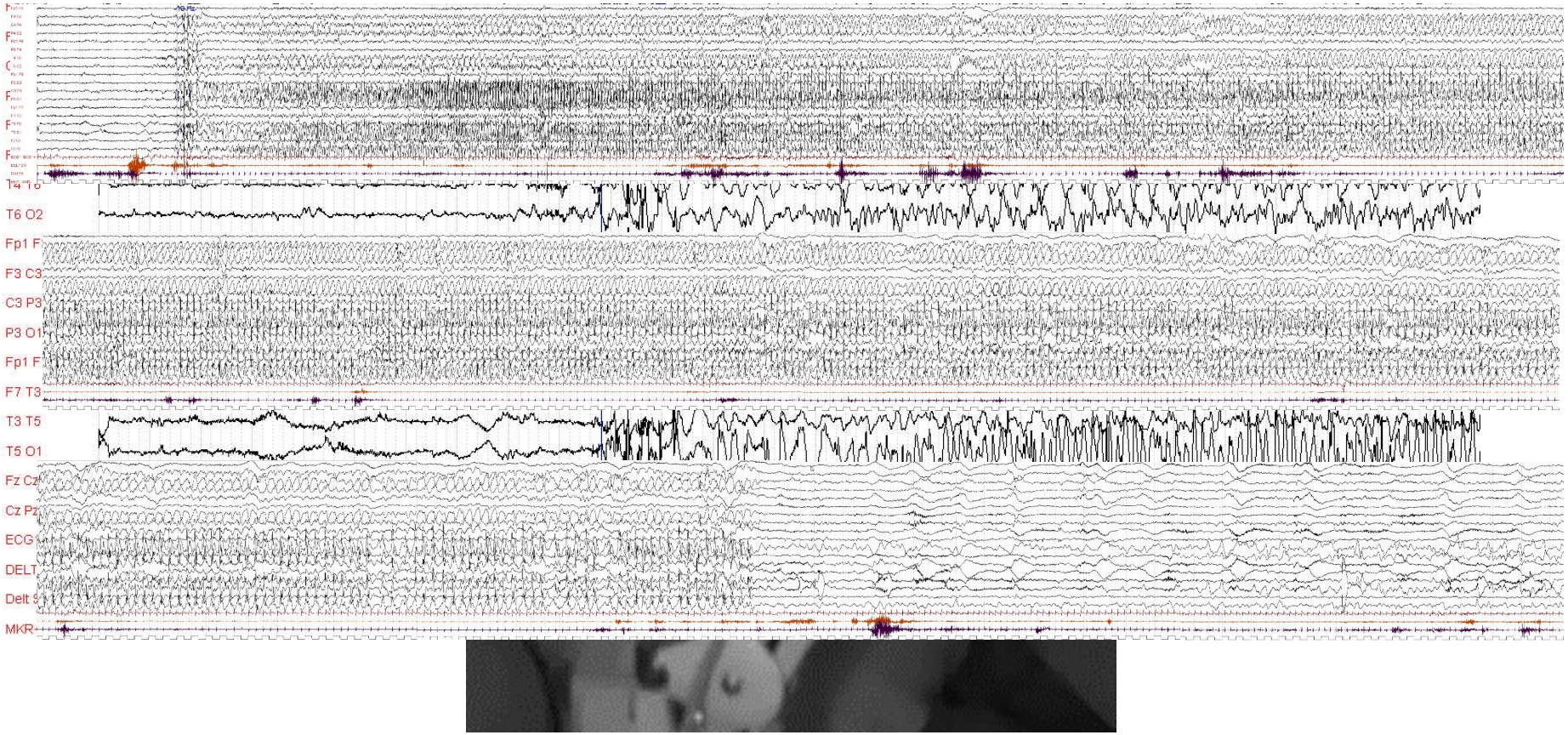
Unilateral brain malformation: hemimegalencephaly

Type of clinical/EEG pattern suggestive of…….



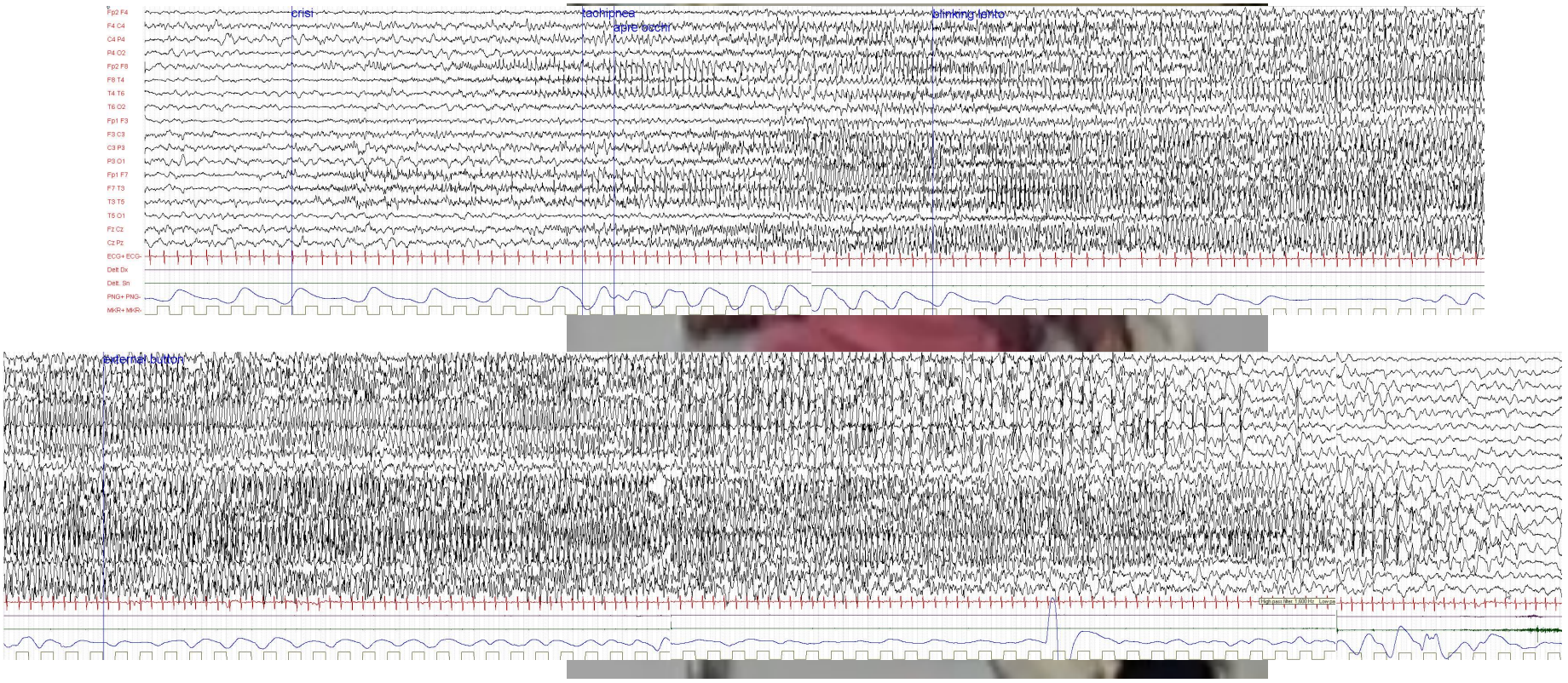
Type of clinical/EEG pattern suggestive of…….

Dravet syndrome, SCN1A mutation

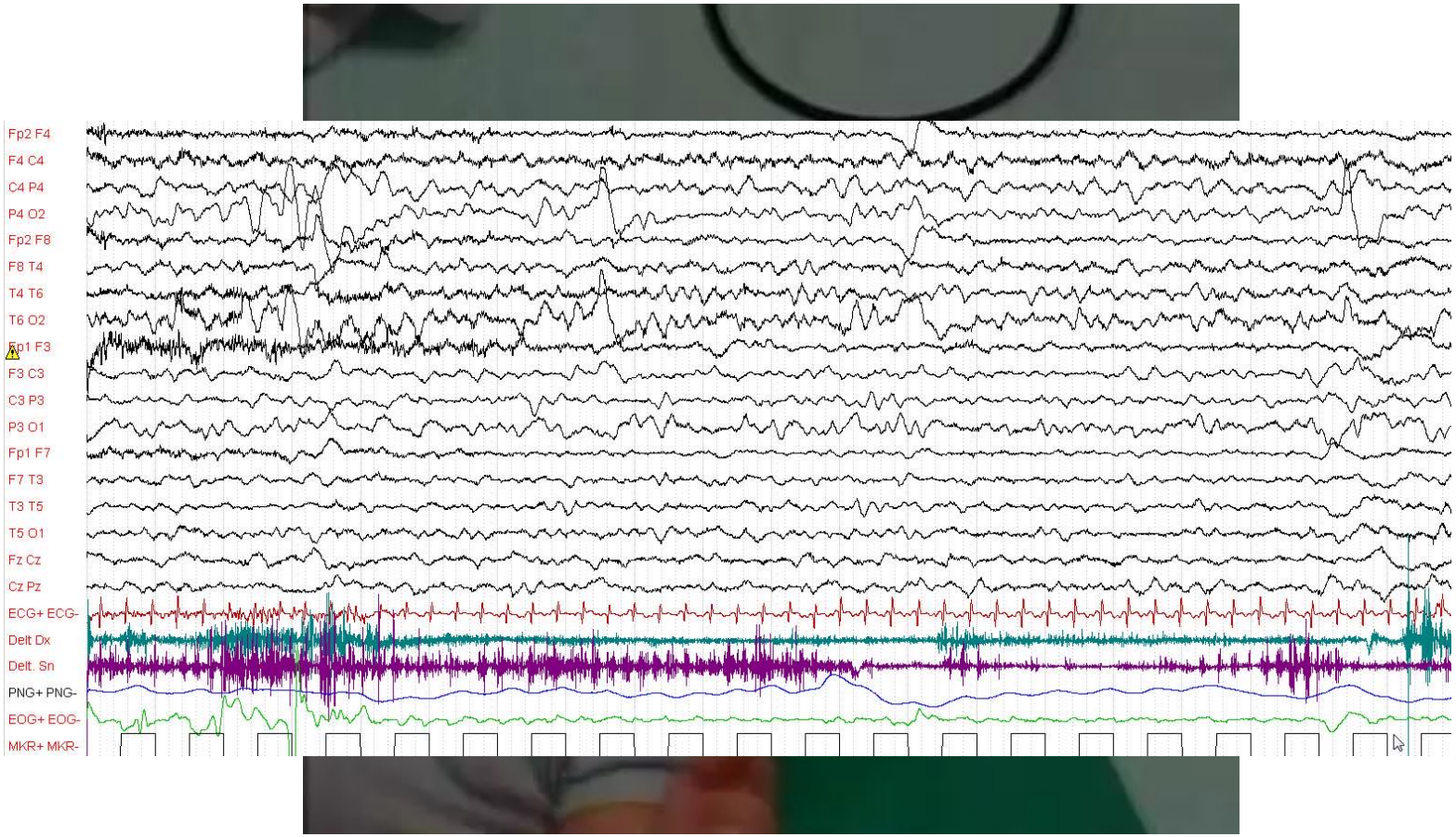


Type of clinical/EEG pattern suggestive of…….

PCDH19 mutation

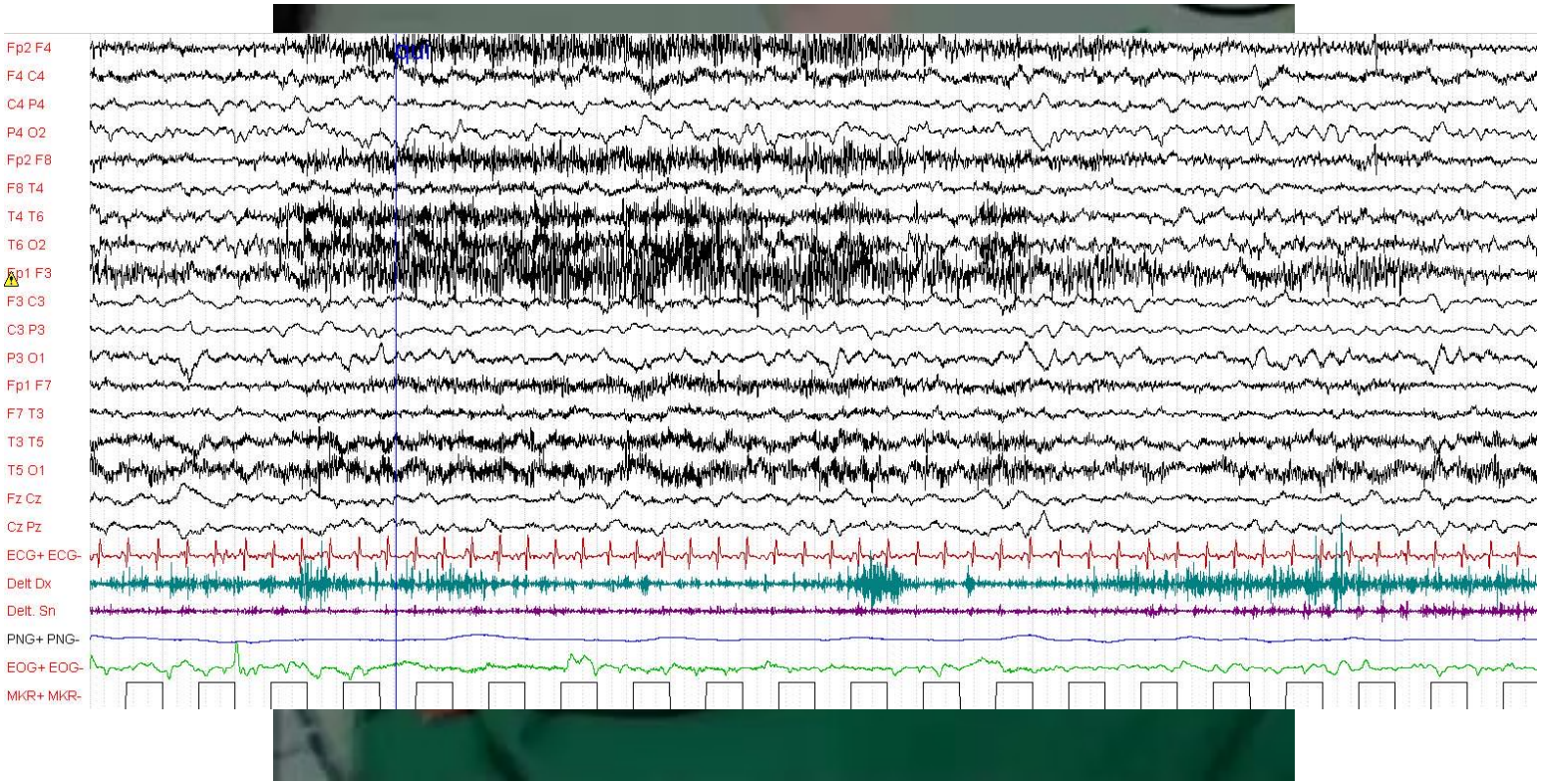


Type of clinical/EEG pattern suggestive of…….



Type of clinical/EEG pattern suggestive of…….

Alternating hemiplegia, ATP1A3 mutation



Dravet Syndrome

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- Epileptic encephalopathy due to *a single* etiological factor (SCN1A – interneuron abnormalities).
- It is characterized by a constant electro-clinical pattern, evolving only in terms of intensity and severity, without any possibility of complete resolution.
- It may be considered as a real disease and a specific nosographic entity.

Electroencephalographic Features in Dravet Syndrome: Five-Year Follow-Up Study in 22 Patients

Journal of Child Neurology
27(4) 439-444

DOI: 10.1177/0883073811419262
http://jcn.sagepub.com
SAGE

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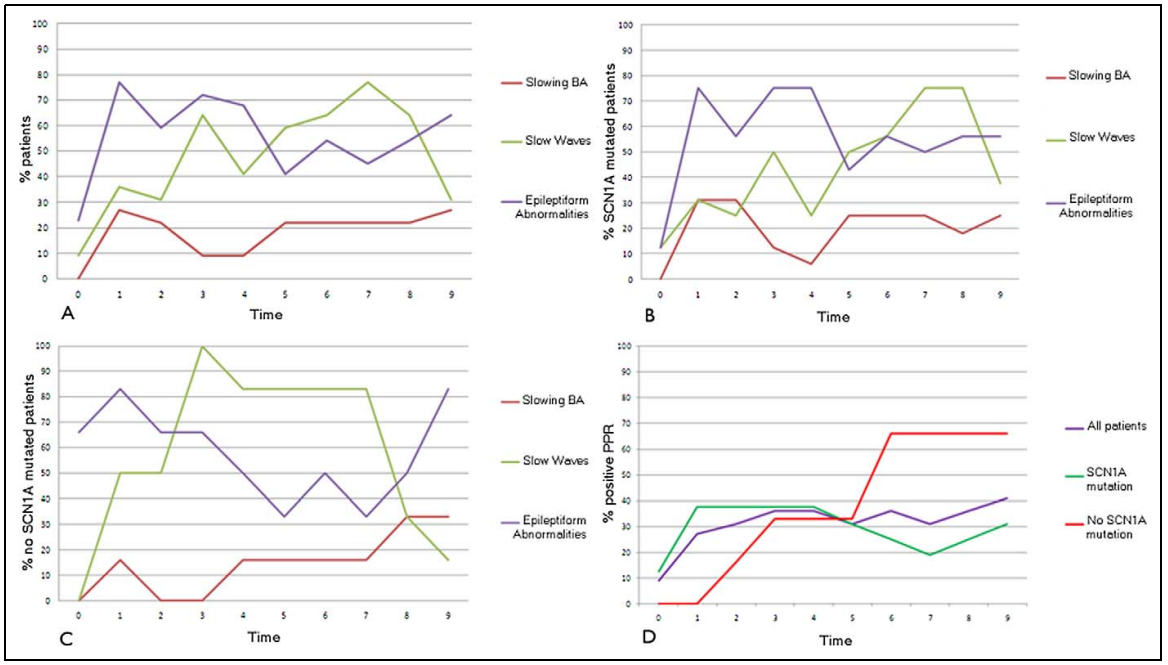

Abstract

The aim of the study was to evaluate interictal electroencephalogram features in 22 patients with Dravet syndrome from the onset of the disease through the next 5 years. Electroencephalogram was abnormal in 5 patients (22.7%) at onset, and in 17 (77.3%) at the end of the study. Epileptiform abnormalities (focal, multifocal, or generalized) were seen in 6 patients at the onset and in 14 (27% vs 64%) at the end of the study. Photoparoxysmal response was present in 41% of patients at the end of follow-up. No statistical differences were found between mutated and nonmutated groups regarding evolution of background activity, interictal abnormalities, and presence of photoparoxysmal response. Electroencephalogram findings seemed to be age dependent, variable among different patients, and not influenced by the presence of sodium channel, voltage-gated, type I, alpha subunit (*SCN1A*) mutation. The lack of specific epileptiform abnormalities contributes to the difficulty of patients' management in Dravet syndrome.

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Bambino Gesù
OSPEDALE PEDIATRICO

Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome

Nathalie Villeneuve [a,b,c], Virginie Laguitton [a], Marine Viellard [b], Anne Lépine [a,c], Brigitte Chabrol [c], Charlotte Dravet [d], Mathieu Milh [c,e,*]

- SCN1A was mutated in 19 out of 21 patients
- After the age of 6 years, **none of the DS patients had a normal intelligence quotient (IQ)**:mean total IQ = 47 ± 3
- They did not find **any significant correlation between the IQ** or developmental quotient assessed between 6 and 10 years of age and the **quantitative and qualitative parameters of epilepsy** during the first two years of life in this small group of patients.

Epilepsia, 52(2):386–392, 2011
doi: 10.1111/j.1528-1167.2010.02925.x

Bambino Gesù
OSPEDALE PEDIATRICO

FULL-LENGTH ORIGINAL RESEARCH

Cognitive development in Dravet syndrome: A retrospective, multicenter study of 26 patients

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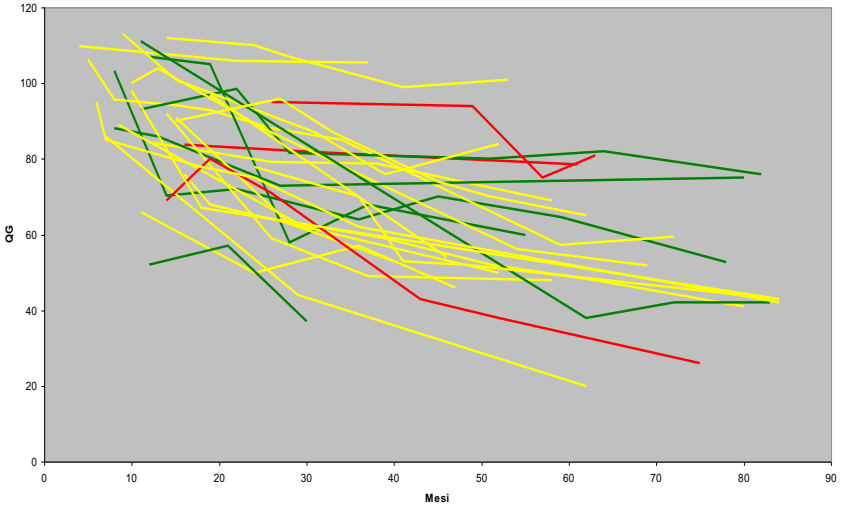
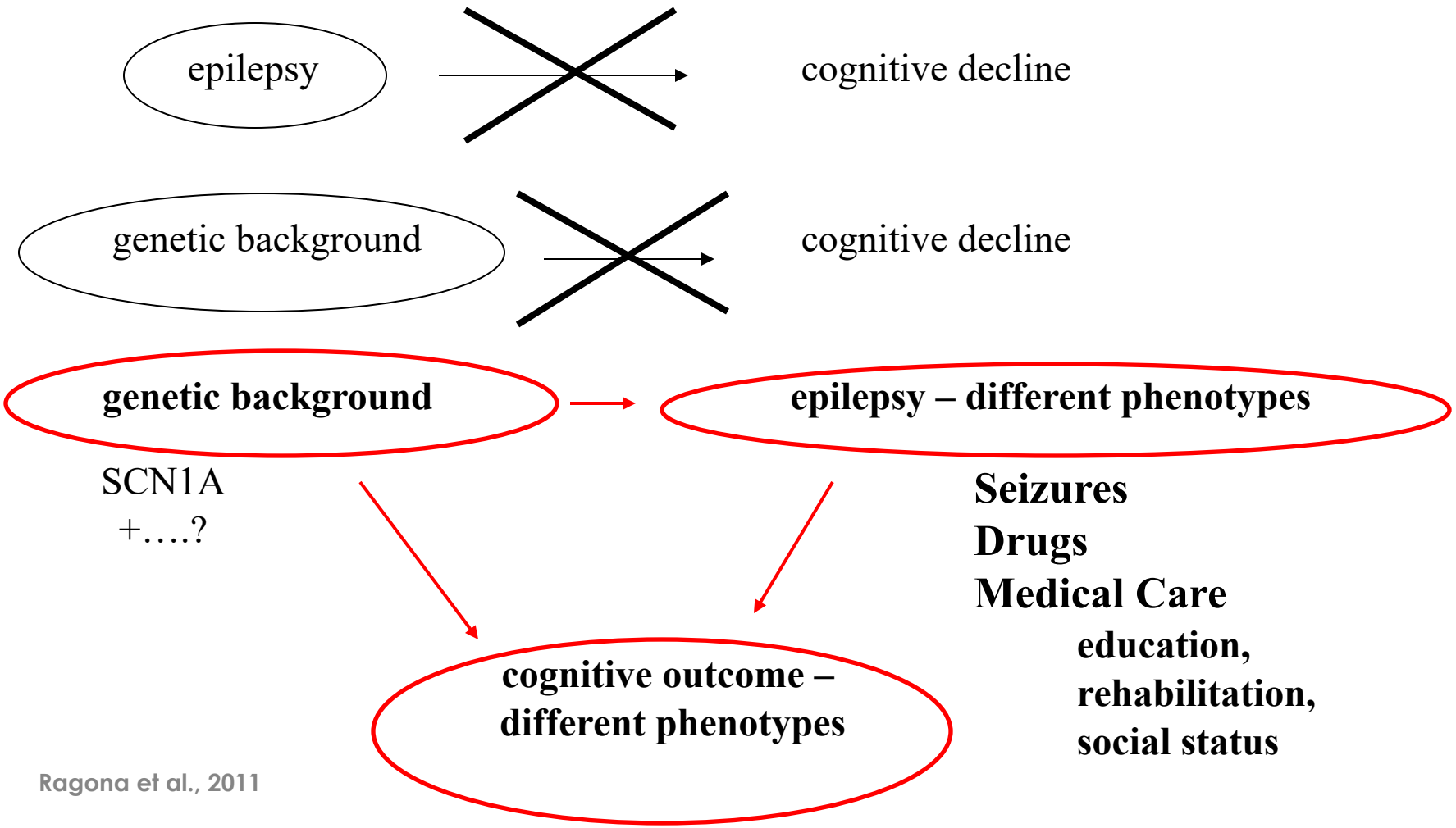
- Truncating mutation in 17 patients
- Missense mutation in 3 patients
- Negative in 6 patients



No differences with regard to the presence and type of mutations

Differences with regard to age: older seems to have worst results than younger

Is there a role for epilepsy and/or genetic background in determining the cognitive outcome?



Ragona et al., 2011

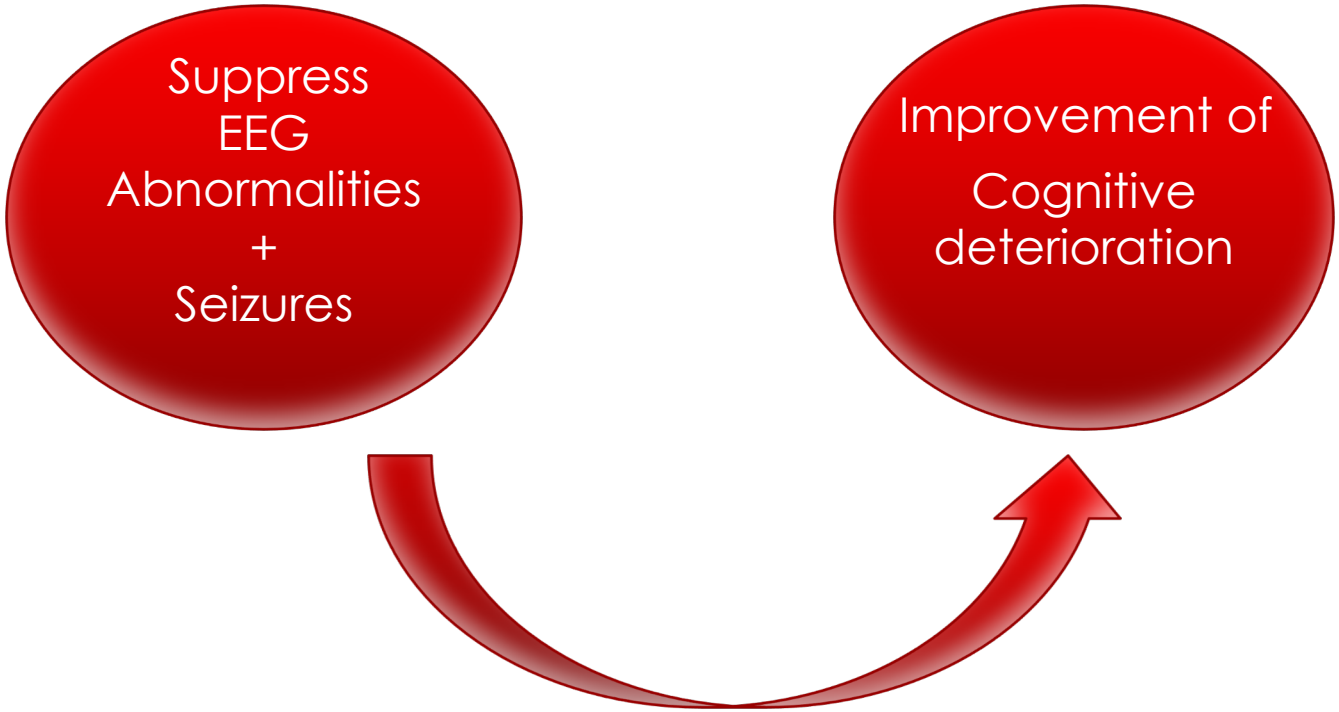
Dravet Syndrome

- "it is not proven that the cognitive decline observed in the first stages of the disease is simply the direct consequence of epilepsy."
- Hypothesis that channelopathy per se can play an important role in the pathogenesis of mental and neurologic deterioration (Dravet et al., 2011).
- Hypothesis that the epileptogenic effects of the SCN1A mutation are mediated by changes in the behavior of inhibitory interneurons in the cortex (Catterall et al., 2010).

Normal development

Epilepsy

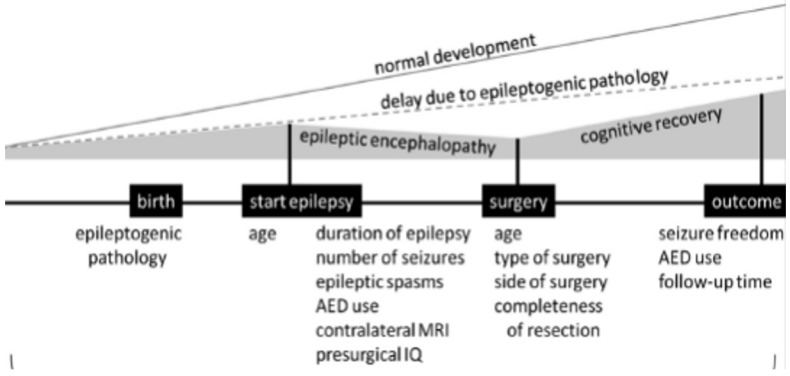
- Epileptic encephalopathy is a dynamic condition not depending from the etiology that may persist over time causing increasingly severe functional effects
- It may improve and remit, either spontaneously or with treatment which suppresses the proposed causative epileptic activity



RESOLUTION OF EPILEPTIC ENCEPAHOPATHY

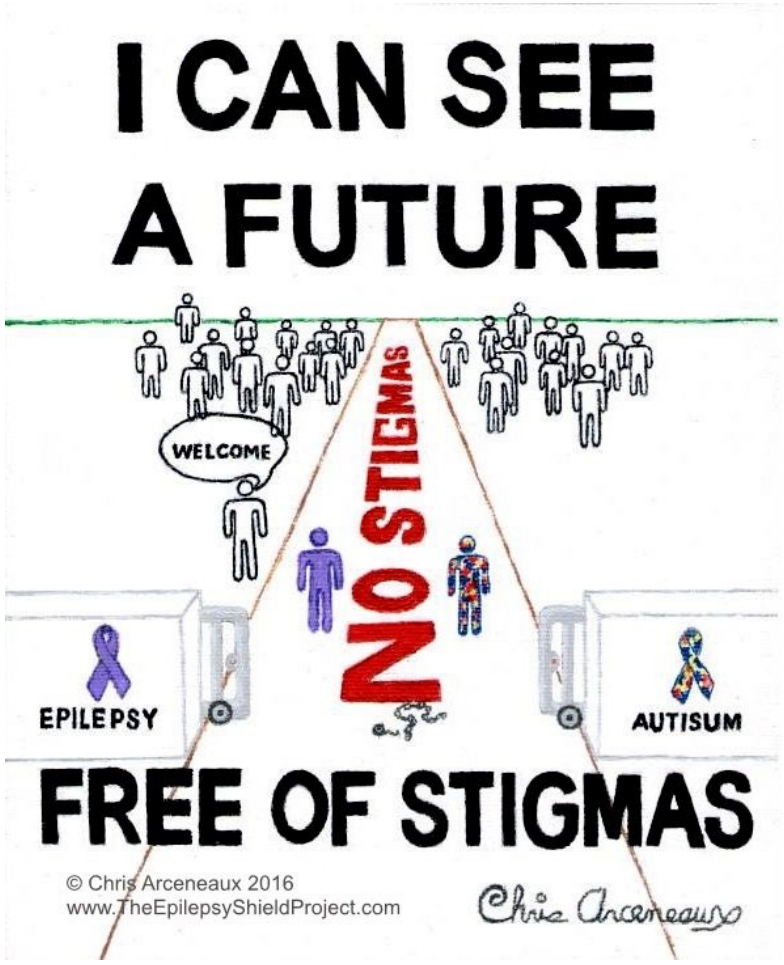
Goals of epilepsy treatment in children

- Complete seizure control
- Low rate of neurological impairment
- AED discontinuation
- Improvement of cognitive and motor functions involved by seizures



Cognitive outcome after epilepsy surgery in children ☆

Monique M.J. Van Schooneveld [b,c,*], Kees P.J. Braun [a,c]



CONTROVERSY IN EPILEPSY

Seizing control of epileptic activity can improve outcome

*Kevin E. Chapman, †Nicola Specchio, ‡Shlomo Shinnar, and §Gregory L. Holmes

Epilepsia, 56(10):1482–1485, 2015
doi: 10.1111/epi.13109

- Frequent epileptic activity (ictal and non-ictal) is harmful to the brain and should be always treated.
- Contribution of abnormal EEG/clinical seizures.
- Epileptic activity is harmful irrespective of epilepsy syndrome or seizure types.
- The epileptic activity independent of the underlying genetic or other etiology does account for worse outcomes.
- Epileptic activity impairs cognitive function globally or selectively above and beyond the underlying pathology alone.
- Treatment of the epileptic activity can improve outcome independent of etiology.

Concept of *Developmental* Epileptic Encephalopathy

- Developmental impact *independent* of epileptic encephalopathy eg. Dravet
- Developmental delay may precede seizure onset
- Many co-morbidities eg. Cerebral palsy, autism spectrum disorder, ID
- Outcome poor even though seizures stop
  eg. KCNQ2, STXBP1 encephalopathies

Scheffer et al., 2016

"Developmental and epileptic encephalopathies"

- Broadening of the terminology, when appropriate, to include the word "developmental" acknowledges that both aspects may be playing a role in the observed clinical presentation. These concepts are critical for families and clinicians to understand the disease process.

- When patients manifest features of both delayed development and very active epileptiform abnormalities, they could be considered to have a "developmental epileptic encephalopathy" to emphasize that both features play a role in their disease.

Scheffer et al., 2016

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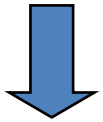
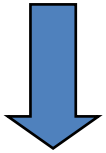
Scheffer et al., 2016

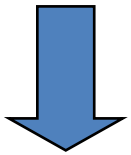
EARLY DIAGNOSIS



EARLY TREATMENT



EARLY CONTROL



IMPROVEMENT IN DEVELOPMENTAL OUTCOME

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