EPILEPTIC ENCEPHALOPATHY

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Definition: epileptic encephalopathy (EE)

- ILAE proposal 2001: a condition where the epileptic abnormalities themselves are believed to contribute to a progressive disturbance in cerebral function
- beyond that expected from their underlying pathology
- Formally recognized in 2006

High risk of EE

- some epileptic syndromes
  : sz that difficult to treat and developmental delay
- early onset epilepsy
  : infantile and childhood period

EE

1. Early myoclonic epilepsy (EME)
2. Ohtahara synd. (EIEE)
3. West synd.
4. Dravet synd.(SMEI)
5. Lennox-Gastaut synd (LGS)
6. Myoclonic status in non-progressive encephalopathy
7. Landau-Kleffner synd (LKS)
8. Epilepsy with continuous spike-waves during slow sleep (CSWS)

Later may be added with

9. Migrating partial seizures in infancy
10. Severe epilepsy with multiple independent spike foci

Catatrophic epilepsy

2010: should not use this term

~~6,9,10~~

EE: 2010

- 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),
- these can worsen over time
- Impairments may be global or more selective, and may occur along a spectrum of severity

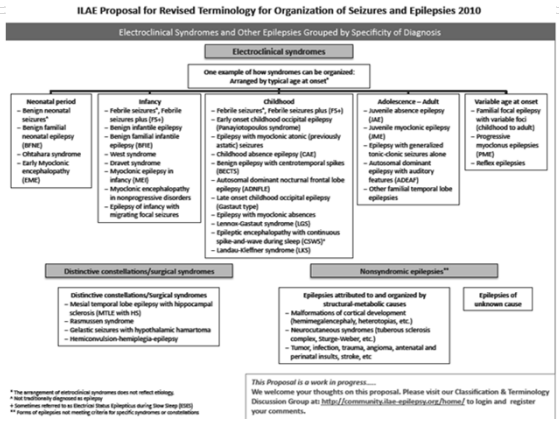
Epilepsia 51(4):676-685,2010

EE

- Devastating epileptic disorders
- Pharmaco-resistant
- Generalized or focal seizures
- Persistent severe EEG abnormalities
- Cognitive dysfunction or decline
- The ictal and interictal epileptiform discharges are age-specific and are the main etiologic factors causing cognitive deterioration

What are the consequences of spikes?

- Even if the spikes are defined as interictal, the cognitive consequences, immediate or in long term, are established in some syndromes
- Animal studies: the epileptiform discharges can impair cognitive abilities through interference with awake learning and memory, as well as memory consolidation during sleep
- The effects appear to be more pronounced if the spikes are very frequent and widespread



Epileptic encephalopathies

Neonatal period
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome

Infancy
- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders

Childhood
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) (including Landau-Kleffner syndrome)
- Lennox-Gastaut syndrome

Other severe epileptic encephalopathies
- Kozhevnikov-Rasmussen syndrome
- Fever-induced refractory epileptic encephalopathy
- Hemiconvulsion-hemiplegia-epilepsy syndrome

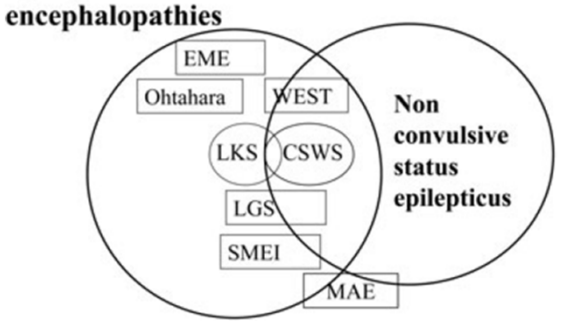
Epilepsia 53(s4) 2012

How to approach EE

Age onset	Seizure	Cause	EEG
• **onset sz**	• **Epileptic syndrome** - Seizure type • **Seizure type** - Convulsive - Non convulsive - Status epilepticus	• **Genetic** +/- metabolic +/- structural • **Structural/ metabolic** • **Cryptogenic**	• **EEG pattern**

Epileptic encephalopathy: is it genetic or is it an accident?

1. Tuberous sclerosis → normal development or developmental delay → no seizure
2. Tuberous sclerosis → normal development or developmental delay → focal sz without cognitive impairment
3. Tuberous sclerosis → normal development or developmental delay → focal sz → epileptic spasms and hypsarrhythmia → cognitive decline



Epilepsia 48(s8):42-3,2007

Discrepancy between clinical manifestations and EEG

Hemipolymicrogyria

- Some may develop a period of developmental regression with electrical status epilepticus of slow sleep (ESES)
- Others have virtual continuous EEG spike and wave over the abnormal hemisphere with virtually no change in cognition

Ohtahara syndrome

- Onset 2 wk to 3 mo

31% occur in day 10

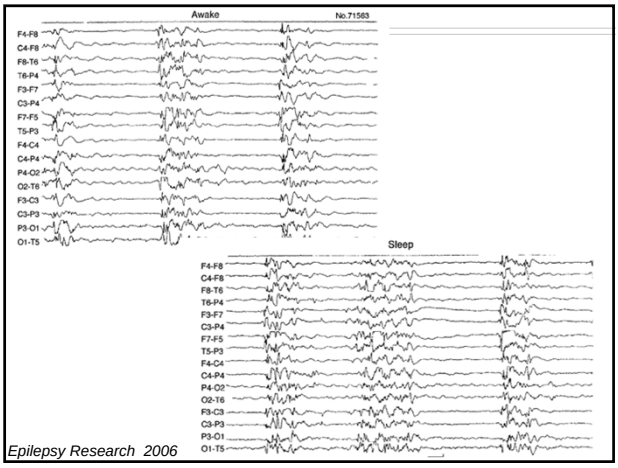
75% occur in one month

1. Tonic spasms
2. Partial motor sz, erratic focal motor sz, hemiconvulsive, GT (30%)
3. Rare myoclonic sz(26%)

Interictal EEG

- SB pattern
- Both waking and sleep
- Regular appearance of periodicity

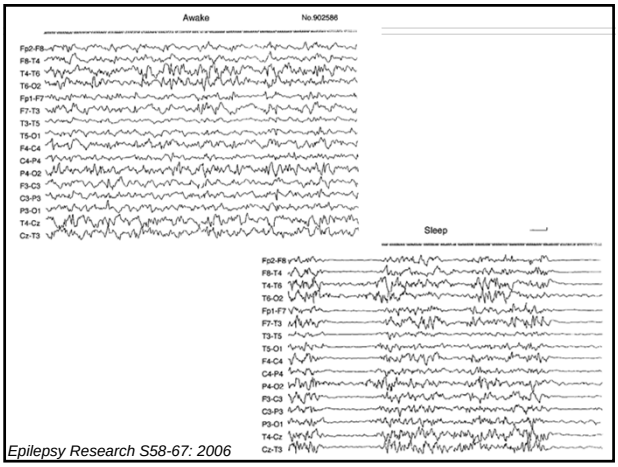
Epilepsy Research S58-67: 2006



Epilepsy Research 2006

EME

- Myoclonia in all, prolonged period
- Throughout the clinical course-partial sz 83%
- Partial sz, tendency to clustering in early period
- Tonic spasms 83% and transient during the course in 66%
- Myoclonia : twitching distal ext or eyelids
- no EEG discharges correspond on EMG
- Most myoclonia → non-epileptic
- SB, prominent in sleep and more pronounce in deep sleep



Epilepsy Research S58-67: 2006

Ohtahara syndrome vs. early myoclonic encephalopathy

	Ohtahara syndrome	EME
Etiology	Organic/symptomatic	Unknown, genetic/metabolic
Seizure type	Tonic spasms, partial	Myoclonic, partial
EEG	Periodic S-B, irrespective of waking and sleeping	S-B
Transition to WS	++	Transient, if any
EEG course of S-B	Transformed into Hyps by age 3–6 months	Long lasting

EME, early myoclonic encephalopathy; S-B, suppression-burst; WS, West syndrome; Hyps, hypsarrhythmia.

Epilepsy Research S58-67: 2006

Ohtahara syndrome

- Can result from a variety of etiologies, majority of cases have been associated with structural brain abnormalities.
- Genetic mutations and metabolic abnormalities have also been described, although at least some of these cases also exhibited associated structural malformation

Structural malformations in EIEE

- Hemimegalencephaly
- Agenesis of corpus callosum
- Porencephaly
- Agenesis of the mamillary bodies
- Dentato-olivary dysplasia
- Hypoxic injury
- Cortical dysplasia
- Cerebral migration disorders
- **Metabolic**: nonketotic hyperglycinemia, Cytochrome C oxidase def, Pyridoxine dependent, Carnitine palmitoyltransferase def, a case of Leigh

Genetic in EE

Mutation Site	Ohtahara Syndrome	EME	West Syndrome	SMEI	Atypical RTT with Early Epilepsy	EFMR
ARX	Yes		Yes			
CDKL5	**Yes**		Yes		Yes	
ErbB4		Yes				
MAGI2			Yes			
PCDH19				Yes		Yes
PNKP	Yes		Yes			
SCN1A				Yes		
SLC25 A22	Yes					
STXBP1	Yes		Yes			

Abbreviations:
EFMR = Epilepsy and mental retardation limited to females
EME = Early myoclonic encephalopathy
RTT = Rett syndrome
SMEI = Severe myoclonic epilepsy of infancy (also known as Dravet syndrome)
Only epileptic encephalopathy syndromes presenting during infancy are included. Some mutations may also be associated with other conditions, e.g., the *SCN1A* mutation is associated with generalized epilepsy with febrile seizures.

Pediatric Neurology 47(2012) 317-323

EME

- Nonketotic hyperglycinemia: large number
- D-glyceric acidemia,
- Proprionic aciduria,
- Molybdenum cofactor def
- Pyridoxine def
- Methylmalonic acidemia
- Sulfite oxidase def
- Menkes syndrome
- Zellweger syndrome

Review

Are early myoclonic encephalopathy (EME) and the Ohtahara syndrome (EIEE) independent of each other?

Aleksandra Djukic [a,b,1], Fred A. Lado [a,*,1], Shlomo Shinnar [a,b], Solomon L. Moshé [a,b,c]

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Epilepsy Research 70S(2006) S68-76

Patient characteristics

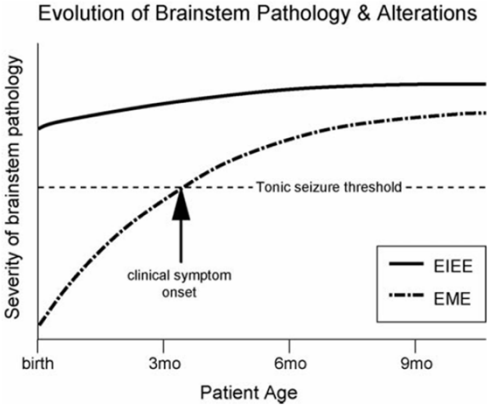
	EIEE	EME
Number of cases	88	30
Gender (F:M)	1:1.2	1:1.3
Etiology		
Structural	27	2
Metabolic	3	13
Cryptogenic	30	15
Presence of both myoclonic and tonic seizures	14 (16%)	22 (73%)
Poor outcome	58 (66%)	22 (73%)

Epilepsy Research 70S(2006) S68-76

Pathological findings on postmortem examination in patients with EIEE and EME

	EIEE (12 patients)	EME (5 patients)	Total (17 patients)
Cortical malformations	8	4	12
White matter abnormalities	3	5	
Basal ganglia pathology	1	3	4
Brain stem pathology	12	5	17
Cerebellum	12	2	14

Epilepsy Research 70S(2006) S68-76



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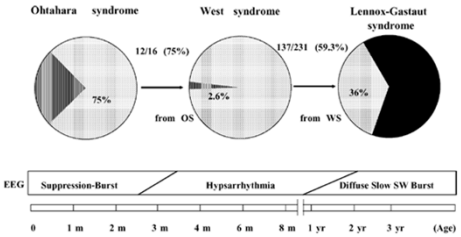


S Ohtahara, Y Yamatogi. Epilepsy Research S58-67: 2006

West syndrome

Triad

- Axial spasms, occuring in clusters
- Hypsarrhythmia
- Psychomotor regression

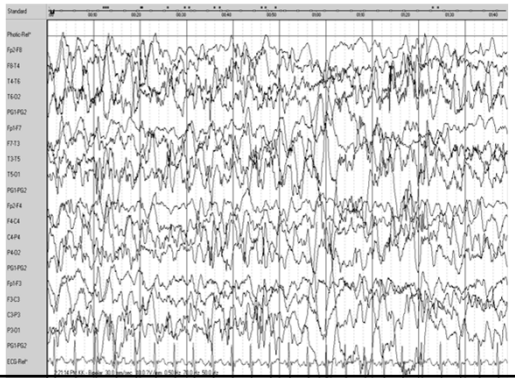
- Onset: between 3-6 months, within 1st year of life in 90%

- Symptomatic causes (75-80%) > Idiopathic > Cryptogenic

West syndrome

Prenatal	Perinatal	Postnatal
• Neurocutaneous synd TSC NF SW IP • Brain dysplasias Aicardi synd Agyria,pachygyria,polymicrogyria Hemimegalencephaly, FCD,schizencephaly • Chromosome anomalies • Congenital infection • HIE • Metabolic, mitochondrial	• HIE • ICH • Infenction • Trauma	• Vt B6 dependency • NKH • MSUD • Biotindase def • PKU • Mitochondrial • Infection • Trauma • Tumor • Degenerative

Interictal EEG: Hypsarrhythmia



Prognosis of West, unfavorable outcome

- Onset age< 3 months
- Psychomotor retardation
- Existence of other seizure types
- Persistence of abnormal EEG features
- Mild to gross neurological deficit
- Significant CT/MRI abnormalities
- Long duration of theraphy

Dravet syndrome: SMEI

Main criteria

- Normal infant
  - Onset in the first year of life
  - severe convulsive seizures
  - first febrile, then afebrile
  - myoclonic jerks ++
  - atypical absences
  - focal seizures
- Slowing down of psychomotor development
- Normal neuroimaing

Clinical course: 3 stages

1. The febrile/diagnostic stage in the first year
   : First seizure related or not to fever, infection, vaccination…
   : Generalized clonic seizure or unilateral hemiclonic sz
   : EEG and other Ix are normal
   :
2. The "worsening" stage between 1-5 years;
   : Period with frequent (alternating hemiclonic) seizures and status epilepticus
   : Other seizures type: myoclonic, atypical absences, focal sz
   : Behavioural deterioration, ataxia

Clinical course: 3 stages

3. Stabilization (after +/- 5 years)
   : Decrease of convulsive seizures duration
   : Secondarily generalized seizures
   : Possible disappearance of myoclonia and absences
   : Decrease of focal seizures
   : Variable cognitive impairment

Dravet syndrome and spectrums

- 1978-1982: Dravet syndrome
- 1987: Incomplete form
- 1992: Kanazawa: High voltage grand mal syndrome
- 1992: Fujiwara et al: Childhood epilepsy with intractable grand mal seizure

- 2001: Claes et al. *SCN1A* mutations
- 2002: Harkin et al. *GABRG2* mutations
- 2006: Suls et al. Microdeletions
- 2009: Patino et al. SCN1B recessive
- Modifiers: 2007 Singh el al. SCN9A.
  2013 Ohmori et al. CACNA1

The spectrum of *SCNIA*-related infantile epileptic encephalopathies

Louise A. Harkin,[1,2] Jacinta M. McMahon,[3] Xenia Iona,[1] Leanne Dibbens,[1,2] James T. Pelekanos,[3] Sameer M. Zuberi,[4] Lynette G. Sadleir,[5] Eva Andermann,[6] Deepak Gill,[7] Kevin Farrell,[8] Mary Connolly,[8] Thorsten Stanley,[5] Michael Harbord,[9] Frederick Andermann,[6] Jing Wang,[10] Sat Dev Batish,[10] Jeffrey G. Jones,[10] William K. Seltzer,[10] Alison Gardner,[1] The Infantile Epileptic Encephalopathy Referral Consortium, Grant Sutherland,[1,2] Samuel F. Berkovic,[3] John C. Mulley[1,11] and Ingrid E. Scheffer[3,12,13]

Brain (2007), 130,843-852

Lennox-Gastaut Syndrome: LGS

- Age onset of LGS is 2-10 years with peaking at 3-5 years
- Mixed epileptic seizures (GT, atypical absence, atonic, myoclonic , GTC)
- Mental retardation

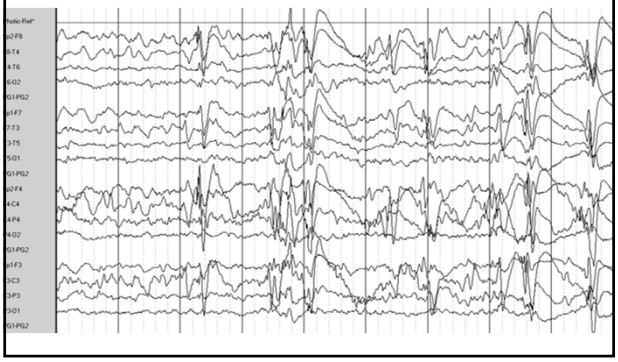
Interictal EEG

: high amplitude slow 1.5-2.5 Hz spike and wave complexes

: focal or multifocal epileptiform discharges may be present

Ictal EEG

: depend on seizure types



LGS

Like West syndrome may be

idiopathic,

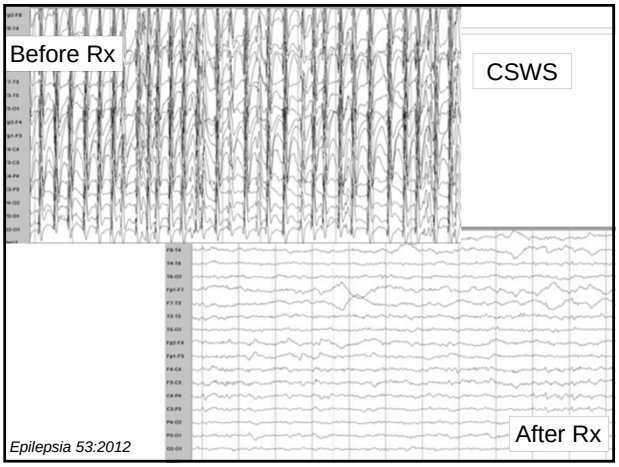
cryptogenic,

symptomatic (70-78%)

LKS, CSWS

- Both syndromes belong to a heterogeneous group of idiopathic (genetic) age related focal epilepsies
- Self-limited
- Linguistic, cognitive and behavioural disturbance and seizures
- Both: continuous spike/wave during sleep, mostly during NREM
- Both: begin in childhood, peak at 4-6 years, remit within teenage years
- Seizures are mainly nocturnal focal motor or GTC
- Attacks are infrequent but may evolve to NCSE or CSE

LKS	CSWS/ESES
• Male predominance • Age onset around 3-8 yrs • A progressive **verbal agnosia** • Associated symptoms: motor hyperactivity, impulsivity, aggressive behavior • Autistic –like may develop	• Male predominance • Age onset around 4-5 yrs • **Neuropsychological regression** (global or selective) • **Motor impairment**
• **Seizure** 70-80%: atypical absence, head drops, 2nd generalized • No seizure 20-30% • **EEG** : slow delta waves, max. temporal : independent multifocal spikes, prominent post^{r} temporal region • Seizure is easy to control but not language • MRI: no structural lesion	• **Seizures** usually occur during sleep; partial motor, GTC or hemiclonic status epilepticus • **EEG** : normal background 75% : focal, multifocal epileptiform discharges in frontotemporal and frontocentral : sleep, > 85% continuous spike/wave activity • MRI: variable developmental abnormalities 50%



The role of genetic workup in early onset EE

1. NB or infants with epileptic spasms, myoclonic sz and drug resistant sz or with status epilepticus
2. Children with progressive worsening clinical course (DD)
3. Children with seizure with movement disorder, dysmorphism, abnormal OFC or genitalia
4. Children with clinical compatible with classic epileptic syndrome (Ohtahara, West, SMEI)
5. Children with specific EEG pattern e.g BS or hypsarrhythmia
6. Children with suggestive abnormalities on MRI

Pediatric Neurology 46 (2012)24-31

Chromosomopathies

Typical phenotypes of

1. 1p36 monosomy
2. Wolf-Hirschhorn syndrome
3. 18q syndrome
4. Angelman syndrome
5. Ring chromosome 20
6. Down syndrome

Pediatric Neurology 46 (2012)24-31

Treatment in EE

- Antiepileptic treatment
- Ketogenic diet: metabolic cause, intractable sz
- Surgery

Epileptic encephalopathy

Not adaptable to surgery	Adaptable to epilepsy Sx
• EIEE	• Rasmussen encephalitis
• EME	• Hemimegalencephaly
• Migrating partial seizure in infancy	• SWS
• West syndrome	• Catastrophic infantile epilepsy due to FCD
• LGS	• Hypothalamic hamartoma
• Doose syndrome	• Startle reflex epilepsy with infantile hemiplegia
• Dravet syndrome	• Temporal lobe epilepsy
• LKS syndrome	

Treatment in EE

- Treating the seizures is necessary BUT in epileptic encephalopathy not sufficient.
- Early ***intensive behavioral intervention*** combined with pharmacotherapy is needed.

Conclusion: EE

- The epileptic activity itself may contribute to severe cognitive and behavioral impairments,
- Worse than what might be expected from the underlying pathology
- Early recognition is important
- Genetic testing:
  - establishes specific etiology
  - alters management decisions
  - predicts prognosis and treatment