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: 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

Later may be added with
9. Migrating partial seizures in infancy
10. Severe epilepsy with multiple independent spike foci

EE

- Devastating epileptic disorders
- Pharmacoresistant
- 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

Epilepsy 51(4):676-685, 2010
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

<table>
<thead>
<tr>
<th>Neonatal period</th>
<th>Early myoclonic encephalopathy (EME)</th>
<th>Ohtahara syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>Epilepsy of infancy with migrating focal seizures</td>
<td>West syndrome</td>
</tr>
<tr>
<td></td>
<td>Dravet syndrome</td>
<td>Myoclonic encephalopathy in nonprogressive disorders</td>
</tr>
<tr>
<td>Childhood</td>
<td>Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)</td>
<td>Including Landau-Kleffner syndrome</td>
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<td></td>
<td>Lennox-Gastaut syndrome</td>
<td>Other severe epileptic encephalopathies</td>
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<tr>
<td></td>
<td>Kazzhenkov-Rasmussen syndrome</td>
<td>Febrile-induced refractory epileptic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Hemiconvulsion-hemiplegia-epilepsy syndrome</td>
<td>Epilepsia 53(s4):2012</td>
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</tbody>
</table>

How to approach EE

<table>
<thead>
<tr>
<th>Age onset</th>
<th>Seizure</th>
<th>Cause</th>
<th>EEG pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>onset sz</td>
<td>Epileptic syndrome</td>
<td>Genetic +/- metabolic +/- structural</td>
<td>EEG pattern</td>
</tr>
<tr>
<td></td>
<td>Seizure type</td>
<td>Structural/ metabolic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizure type</td>
<td>Cryptogenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Convulsive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non convulsive</td>
<td></td>
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<tr>
<td></td>
<td>Status epilepticus</td>
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</tr>
</tbody>
</table>

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 hypsarhythmia ⇒ cognitive decline.

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

- Tuberous sclerosis ⇒ normal development or developmental delay ⇒ no seizure.

- Focal seizures without cognitive impairment.

- Epileptic spasms and hypsarhythmia ⇒ cognitive decline.
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
- Interictal EEG
  1. Tonic spasms
  2. Partial motor sz, erratic focal motor sz, hemiconvulsive, GT (30%)
  3. Rare myoclonic sz (26%)

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 pronounced in deep sleep

Ohtahara syndrome vs. early myoclonic encephalopathy

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

EME, early myoclonic encephalopathy; S-B, suppression-burst; WS, West syndrome; Hyps, hypsarrhythmia.
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 palmityltransferase def, a case of Leigh

Genetic in EIEE

<table>
<thead>
<tr>
<th>Mutation Site</th>
<th>Ohtahara Syndrome</th>
<th>EME</th>
<th>Wex syndrome</th>
<th>SMID</th>
<th>Atypical RTT</th>
<th>EFMR</th>
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<tbody>
<tr>
<td>AEX</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKL5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>RHHD</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>MAGO2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>PCDH19</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<td>PNCP</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>SCN1A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>SLC2A5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
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<tr>
<td>STXBP1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>

Annotations:
- EME = Early myoclonic encephalopathy
- SMID = Severe myoclonic encephalopathy 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 associatedwith generalized epilepsy with febrile seizures.

EME

- Nonketotic hyperglycinemia: large number
- D-glyceric acidemia,
- Propionic 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?

Alessandra Ditta,1,2,3,4 Fred A. Lado,4-6,1, Shilomo Shinar4-6, Solomon L. Muro,4-6,1

1 Department of Neurology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA
2 Department of Pediatrics, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA
3 Department of Neurosciences, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA

Patient characteristics

<table>
<thead>
<tr>
<th>EIEE</th>
<th>EME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>88</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>1:1.2</td>
</tr>
</tbody>
</table>

Etiology

| Structural | 29 | 2 |
| Metabolic | 3 | 13 |
| Cryptogenic | 30 | 15 |

Presence of both myoclonic and tonic seizures

<table>
<thead>
<tr>
<th>EIEE</th>
<th>EME</th>
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<tbody>
<tr>
<td>14(16%)</td>
<td>22(73%)</td>
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</table>

Poor outcome

<table>
<thead>
<tr>
<th>EIEE</th>
<th>EME</th>
</tr>
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<tbody>
<tr>
<td>58(66%)</td>
<td>22(73%)</td>
</tr>
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</table>
West syndrome

**Triad**
- Axial spasms, occurring 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**

### Pathological findings on postmortem examination in patients with EIEE and EME

<table>
<thead>
<tr>
<th></th>
<th>EIEE (12 patients)</th>
<th>EME (5 patients)</th>
<th>Total (17 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical malformations</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>White matter abnormalities</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia pathology</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Brain stem pathology</td>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

**Evolution of Brainstem Pathology & Alterations**

- Severity of brainstem pathology
- Tonic seizure threshold
- Clinical symptom onset

**Prenatal**
- Neurocutaneous synd
- TSC
- NF
- SW
- IP
- Brain dysplasias
- Aicardi syndrome
- Agyria, pachygyria, polymicrogyria
- Hemimegalencephaly
- FCD, schizencephaly
- Chromosome anomalies
- Congenital infection
- HIE
- Metabolic, mitochondrial

**Perinatal**
- HIE
- Infection
- Trauma

**Postnatal**
- 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 therapy

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 neuroimaging

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 et al. SCN9A
  2013 Ohmori et al. CACNA1

The spectrum of SCN1A-related infantile epileptic encephalopathies

- Leslie A. Harkin,1,3 Janine M. McKibbin,1 Xenia Iora,1 Leanne Dibben,1,3 James T. Paterson,3
- Simon M. Zuberi,1 Lynette G. Sudlow1,2 Eva Andersson,1,3 Dagob G. Stobbe,1,3 Kevin Farrell,1,3 Mary Connolly,1
- Therese Scadding,1 Michelle Harrison,1,2 Frederick Anderson,1,3 Jing Wang,8 Yu Deng,9,10
- Jeffrey G. Jones,8 William K. Setaro,11 Alison Gardner12 The Infantile Epileptic Encephalopathy Referral Consortium.

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

<table>
<thead>
<tr>
<th>LKS</th>
<th>CSWS/SESE</th>
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<tbody>
<tr>
<td>- Male predominance</td>
<td></td>
</tr>
<tr>
<td>- Age onset around 3-8 yrs</td>
<td></td>
</tr>
<tr>
<td>- A progressive verbal agnosia</td>
<td></td>
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<tr>
<td>- Associated symptoms, motor hyperactivity, impulsivity, aggressive behavior</td>
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<tr>
<td>- Autistic-like may develop</td>
<td></td>
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<tr>
<td>- Seizure 70-80%: atypical absence, head drops, 2nd generalized</td>
<td></td>
</tr>
<tr>
<td>- No seizure 20-30%</td>
<td></td>
</tr>
<tr>
<td>- EEG</td>
<td></td>
</tr>
<tr>
<td>: slow delta waves, max. temporal</td>
<td></td>
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<tr>
<td>: independent multifocal spikes, prominent post temporal region</td>
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<tr>
<td>- Seizure is easy to control but not language</td>
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</tr>
<tr>
<td>- MRI: no structural lesion</td>
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<tr>
<td>- Male predominance</td>
<td></td>
</tr>
<tr>
<td>- Age onset around 4-5 yrs</td>
<td></td>
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<tr>
<td>- Neuropsychological regression (global or selective)</td>
<td></td>
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<tr>
<td>- Motor impairment</td>
<td></td>
</tr>
<tr>
<td>- Seizures usually occur during sleep; partial motor, GTC or hemiconic status epilepticus</td>
<td></td>
</tr>
<tr>
<td>- EEG</td>
<td></td>
</tr>
<tr>
<td>: normal background 75%</td>
<td></td>
</tr>
<tr>
<td>: focal, multifocal epileptiform discharges in frontotemporal and frontocentral</td>
<td></td>
</tr>
<tr>
<td>: sleep, &gt; 85% continuous spike/wave activity</td>
<td></td>
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<tr>
<td>- MRI: variable developmental abnormalities 90%</td>
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</tbody>
</table>
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

Chromosomopathies

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

Treatment in EE

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

Epileptic encephalopathy

Not adaptable to surgery
- EIEE
- EME
- Migrating partial seizure in infancy
- West syndrome
- LGS
- Doose syndrome
- Dravet syndrome
- LKS syndrome

Adaptable to epilepsy Sx
- Rasmussen encephalitis
- Hemimegalencephaly
- SWS
- Catastrophic infantile epilepsy due to FCD
- Hypothalamic hamartoma
- Startle reflex epilepsy with infantile hemiplegia
- Temporal lobe epilepsy

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

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