EEG in Infantile Genetic Epilepsies

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Disclosures

• Co-PI Cleveland Clinic CDKL5 Center of Excellence

• Clinical trials:
  • Marigold study
  • Eisai 338
Goals

• 1. EEG helps us with the diagnosis of infantile genetic epilepsies

• 2. Electroclinical syndromes guide us in the treatment of infantile genetic epilepsies

• 3. Interpretation of the EEG must past beyond the visual analysis to move from electroclinical syndromes to specific genetic entities
Hans Berger
German psychiatrist

Hans Berger was a German psychiatrist. He is best known as the inventor of electroencephalography in 1924, coining the name, and as the discoverer of the alpha wave rhythm, also known as the "Berger wave". Wikipedia

Born: May 21, 1873, Coburg, Germany
Died: June 1, 1941, Jena, Germany
Citations: 2,052
Education: University of Jena
Field: Psychiatry
Electroclinical Syndromes

- Age
- Seizure Types
- Neurocognitive Status

EEG findings
Historical Overview of the Electro clinical syndromes

• From 1947 - William G Lennox and Henri Gastaut describes the association of different seizures and the EEG findings in LGS
• Epilepsy with Continuous Spike and Wave during slow wave sleep was
  • First recognized by Landau and Kleffner in the 1950s (Landau WM, Kleffner FR Neurology 1957)
  • Described in by Tassinari’s group in 1970s (Patry G et al. Arch Neurol 1971)
• 1970s - Ohtahara S et. al. detailed the features of early infantile epileptic encephalopathy with suppression-burst. (Ohtahara S et al. No to Hattusu 1976)
• 1978 - Charlotte Dravet described Dravet Syndrome (La Vie Médicale 1978; 8: 543-8)
• 1984 - Hrachovy et al described the EEG variations of hypsarrhythmia
• 1995- Migrating Focal Epilepsy of Infancy was initially described by Coppola et al (Coppola et al. Epilepsia 1995; 36:1017-24)
Electro-clinical syndromes associated to genetic conditions – Genetic etiologies

• Neonate and Infant
  • Ohtahara syndrome
  • Early Myoclonic Encephalopathy
  • Epilepsy of Infancy with Migrating Focal Seizures
  • West syndrome
  • Dravet syndrome

• Childhood
  • Lennox Gastaut Syndrome
  • CSWS/LKS
Limitations of the EEG

• High sensitivity

• Low specificity

• Variable inter-rater reliability
  • Low for hypsarrhythmia (k=0.40) (Hussain SA et al. Epilepsia 2015)
  • High for high amplitude slow waves during sleep in normal children 3-18 months (Mytinger JR et al. J Clin Neurophysiol 2018)
EEG findings in the Infantile Genetic Epilepsies
Ohtahara syndrome and Early Myoclonic Encephalopathy
Ohtahara syndrome and Early Myoclonic Encephalopathy

- ARX
- CDKL5
- SLC25A22
- STXBP1
- SPTAN1
- KCNQ2
- ARHGEF9
- PCDH19

- PNKP
- SCN2A
- PLCB1
- SCN8A
- ST3GAL3
- TBC1D24
- BRAT1
- Others

Source: OMIM
Epilepsy of Infancy With Migrating Focal Seizures
Epilepsy of Infancy with Migrating Focal Seizures – Genetic etiology

• Multiple genes describes as causative
  • SCN1A (Freilich ER et al. Arch Neurol 2011; 68:665-671)
  • KCNT1 (Barcia G et al. Nat Genet 2012; 44:125-1259)
  • PLCB1 (Poduri A et al. Epilepsia 2012; 53:3146-150)
  • SLC25A22 (Poduri A et al Ann Neurol 2013; 74: 873-882)
  • TBC1D24 (Milh M et al. Hum Mutat 2013;34:869-72)
  • SCN2A (Dhamija R et al. Pediatr Neurol 2013; 49:486-488)
  • SCN8A (Ohba C et al. Epilepsia 2014; 55(7): 994-1000)
  • 47XYY (Iyers RS et al. Epilepsy Behan Case Rep 2014; 20(2)43-5)
  • ?? (De Pilippo MR et al. Epilepsy res 2014; 108(2):340-4)
  • Multiple sodium channel gene deletion SCN1A, SCN2A, SCN3A, SCN7A, SCN9A
    (Lim BC et al. Epilepsy Res 2015;109:34-9)
West syndrome
<table>
<thead>
<tr>
<th>Etiological classification</th>
<th>Categories</th>
<th>Specific etiologies or lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>CNS Malformations</td>
<td>Cortical Dysplasia, Cerebral Dysgenesis, Lejeune Syndrome, Lissencephaly, Le Miller-Dieker syndrome, Holoprosencephaly</td>
</tr>
</tbody>
</table>

**Genetic Mutations**

- ARX
- CDKL5
- MEF2C
- SLC25A22
- SPTAN1
- STXBP1
- SCN2A
- GRIND2A
- FOXG1
- CASK
- ALG13
- PNPO
- ADSL
- PHACTR1
- PLCB1

Other conditions:
- Pyruvate dehydrogenase complex deficiency
- Leigh syndrome
- Mecolismena
- Pyridoxine deficiency
- Urea cycle disorders
- Congenital disorders of glycosylation
Dravet syndrome
Lennox Gastaut Syndrome
Lennox Gastaut Syndrome – Genetic CDKL5 Deficiency Disorder
Electroclinical Syndromes = Treatment

- Age
- Seizure Types
- Neurocognitive Status

EEG findings
**NICE: AED Guidelines**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; line AED</th>
<th>Adjunctive AEDs</th>
<th>AEDs that may worsen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile Spasms-‐non TSC</td>
<td>ACTH Oral Steroids</td>
<td>Ketogenic Diet Valproate Topiramate, Zonisamide Clonazepam</td>
<td></td>
</tr>
<tr>
<td>Infantile Spasms-‐TSC</td>
<td>Vigabatrin</td>
<td>ACTH Oral Steroids As above</td>
<td></td>
</tr>
<tr>
<td>Dravet Syndrome</td>
<td>Valproate Topiramate</td>
<td>Clobazam Stiripentol</td>
<td>CBZ, OXZ, LTG, PHT, Vigabatrin, Gabapentin</td>
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</tbody>
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*National Institute for Clinical Excellence (NICE), UK*
NICE: AED Guidelines

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<tr>
<td>Early Infantile Epileptic Encephalopathy</td>
<td>Oral Steroids Levetriacetam</td>
<td>Ketogenic Diet Topiramate, Zonisamide VGB, Phenobarbital</td>
<td></td>
</tr>
<tr>
<td>LGS</td>
<td>Valproate</td>
<td>Lamotrigine Clobazam Steroids Rufinamide Levetriacetam Felbamate, KD</td>
<td>CBZ, OXZ, VGB Gabapentin</td>
</tr>
<tr>
<td>CSWS</td>
<td>Steroids Benzodiazepines</td>
<td>Valproate Ethosuximide LTG, LEV, KD</td>
<td>CBZ, OXZ, PHT, PHB</td>
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Adapted and modified from National Institute for Clinical Excellence (NICE) guidelines CG137 (National Institute for Clinical Excellence, 2012) and from McTague A and Cross JH (2013).
What is treatment Response?

1. Seizures
   All or None seizures

2. EEG
   Resolution of IED

3. Development
   Not Easy To Assess
How to evaluate response to treatment?

• Complete cessation of spasms confirmed by video-EEG
  • Learning point 1: what spasms look like?
• Abolition of hypsarrhythmia on prolonged EEG
  • Learning point 2: what hypsarrhythmia looks like?

AAN and CNS Practice Parameters
Mackay MT et al. Neurology 2004; 62: 1168-81
EEG Elements that Define Electroclinical Syndromes

Interictal Epileptiform Discharges

Ictal Patterns
Can the EEG be more specific?

Infantile Spasms due to Brain Structural Lesions

Infantile Spasms due to Genetic Etiology
What about other elements of the EEG?

3 months 21 days infant girls with CDD

Will these findings point us to CDD?

We don’t know yet!
Could these findings be indicative of a genetic etiology?

May be!

1 year 4 months girls with STXBP1 encephalopathy
Tang Y et al. submitted for publication
How the EEG can do better to go from electroclinical syndromes to specific etiological groups or diseases?
Hypsarrhythmia? Yes or not " "

3 months 21 days infant girls with CDD
Quantitative EEG analysis AND Visual EEG analysis

-Epilepsy of infancy with migrating focal seizures (EIMFS)
-Dravet syndrome
-Benign Familial Neonatal Epilepsy (BFNE)
-Structural focal epilepsy with temporo-occipital seizures (SFTOS).
Slow Seizure Propagation from one electrode to other

Seizure patterns in EIMFS might result from “diffusing oil spots” though intracortical propagation and migration through white matter propagation. Therefore, migration could be defined as a particular propagation of an ictal activity through white matter fibers, leading to the initiation of a second ictal activity.

Low synchronization in the evolution of the seizure with adjacent electrodes
Future directions

**EEG in Electro-clinical diagnosis**

- Visual analysis
- Quantitative analysis
- Enhanced Visual analysis

**The Benefits!**

- Seizure outcome
- Developmental outcome
- Quantitative EEG as biomarker
Questions