Typical and Atypical Epilepsy
Phenotypes of Amenably Treatable
Infantile Epilepsies

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Disclosure

None

Most of the therapies mentioned for the rare disorders I present are not FDA approved
Learning Objectives

• Recognize the spectrum of presentations of amenably treatable infantile epileptic encephalopathies:
  • Things are not always what they seem
• Develop strategies to diagnose such disorders in the clinic
  • Make it simple
Outline

Vitamin Responsive Syndromes
Other Disorders
Clinical Approach and Utility
Presentations of Biotinidase Deficiency

- Symptoms usually begin at 2 to 3 months of age and consist of: seizures (which can be generalized tonic-clonic, myoclonic, or infantile spasms), hypotonia, episodic ataxia, respiratory disturbances, high-frequency hearing loss, optic atrophy, and developmental delay dermatitis, alopecia, conjunctivitis, and chronic candidiasis.

- We reported the occurrence of Biotinidase deficiency with infantile spasms and mental delay without rash or other Sxs.

Presentations of Biotinidase Deficiency

New Insights

• Bunch et al. reported occurrence of frontal subcortical cysts, mega cisterna magna with generalized epilepsy

• Singhi and Ray reported presentation as Ohtahara syndrome.

• Krishanakumar et al. reported presentation with low CSF glucose and high lactate ~ to GLUT1 deficiency

The syndrome of Biotin/Thiamine Responsive Epilepsy

- Ozand: autosomal recessive, dystonia seizures and neurological deterioration due to SLC19A3 mutation with onset in childhood and response to out to both Biotin (dose: 2-3mg/kg) and Thiamine (100-300mg/d).

- We described a infantile onset milder form with mild neonatal seizures mild delay and reversal of MRI changes on Biotin.

- Yamada: severe infantile (2-11 m) form epileptic spasms cerebral-cerebellar atrophy, increased signal in basal ganglia, thalami multifocal spikes, no hypsarrhythmia.

Cerebral Folate Deficiency

- **Etiology:** mutations in the FOLR1 (folate receptor alpha gene), blocking antibodies for folate receptors or secondary to mitochondrial disorders, Rheumatoid arthritis, Rett, autism.
- **Onset:** 4-6 months of age with delay in development, hypotonia, and ataxia, dyskinesias (choreo-athetosis, hemiballismus), spasticity, epilepsy and a times progressive encephalopathy.
- **Treatment** of the condition with folinic acid 0.5-3 mg/kg/day.

Cerebral Folate Deficiency
Recent Insights

- **Seizures:** myoclonic astatic, tonic, myoclonic, rarely focal
- **EEG:** Generalized 3-4 Hz SSW, multifocal spikes
- We reported occurrence of *infantile spasms* and of electrical status epilepticus, *ESES*, in sleep as epileptic manifestation of cerebral folate deficiency

Pyridoxine Dependent Epilepsy

- Seizures: partial + generalization, myoclonic, atonic.
- Transient response to AEDs was observed
- An early encephalopathy with an apparent ocular apraxia
- EEG: Suppression burst, Generalized irregular SSW, uni or bilateral EEG szs, multifocal spikes, hysarrhythmia
Pyridoxine Dependent Epilepsy
Recent Insights

- We reported that EEG burst suppression may fluctuate for up to 5 days after start of therapy
- Others reported presence of cerebral atrophy, mega cisterna magna hydrocephalus, FCD and thin posterior CC common (abnormal MRI in half)
- Low lysine diet, folic acid (folinic responsive szs allelic)

Pyridoxine Responsive Seizures

• The UK survey identified infants and children who responded to pyridoxine and in whom it was later discontinued without recurrence

• Some children with infantile spasms respond to pyridoxine (12% in largest series)

• Struys et al reported 2 sibs with B6-responsive szs and increased urinary α-AASA. Subsequent studies: molybdenum cofactor deficiency due to homozygous MOCS2 mutation.

Struys EA et al. ,Pediatrics 2012;130:e1716; Netherlands
Pyridoxal-5-Phosphosphate Dependent Epilepsy

• Presents neonatally with mostly myoclonic, but also tonic, and clonic, seizures and status epilepticus with burst suppression pattern on EEG.

• We reported the occurrence of neonatal tonic SE, of focal SE and of ESES in P5P dependent epilepsy

Outline

Vitamin Responsive Syndromes

Other Disorders

Clinical Approach and Utility
Brain Malformations in Inborn Errors of Metabolism

- Agenesis of the corpus callosum has been reported with peroxisomal disorders, mitochondrial disease, maternal phenylketonuria, nonketotic hyperglycinemia, and Smith-Lemli-Opitz
- Mitochondrial disease: Cortical dysplasia, heterotopias, aplasia of the corticospinal tracts dysplasia of inferior olive
- SCAD: We reported a case of short-chain acyl-coenzyme A dehydrogenase deficiency with West syndrome, frontal meningocele, abnormal cortical gyration, and partial corpus callosum agenesis

Presentations of EAST Syndrome

- **KCNJ10** (Kir4.1) encodes an inwardly rectifying K channel
- Presents first with GTCs in the infancy and later patients develop hyokalemic alkalosis ataxia and sensorineural hearing loss as they fail to speak or walk
- **MRI:** increased signal in CBL nuclei, thin cord

Neurological features of epilepsy, ataxia, sensorineural deafness, tubulopathy syndrome
Favorable Outcome in Molybdenum Cofactor Type A Deficiency Treated With cPMP

- Newborn started on a daily cPMP dose of 80 mg/kg at 4 hours of age normalized S-sulfocysteine, uric acid, and xanthine levels
- Therapy stopped seizures prevented regression normalized exam and almost normalized long term outcome at 21 m.

Hitzet M et al. Pediatrics 2012;130:e1005–e1010Groningen
CSF Neurotransmitter Disorders

• **Presentation:** developmental delay, movement disorders and epilepsy

• **Therapy:** Often benefit from one or more of: L-Dopa, tetrahydrobiopterin, tryptophan, folinic acid

<table>
<thead>
<tr>
<th></th>
<th>Phe (plasma)</th>
<th>Biopterin (urine)</th>
<th>Neopterin (urine)</th>
<th>DHPR (blood)</th>
<th>HVA (CSF)</th>
<th>5-HIAA (CSF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTPCH1 (recessive)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>GTPCH1 (dominant)</td>
<td>N</td>
<td>N (↑ CSF)</td>
<td>N (↑ CSF)</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>PTPS</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
<td>±↓</td>
</tr>
<tr>
<td>PCD</td>
<td>↑</td>
<td>↓</td>
<td>Normal ↓ primapterin</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>DHPR</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>SR</td>
<td>N</td>
<td>N (↑ CSF)</td>
<td>N (↑ CSF sepiapterin)</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

N, normal; Phe, phenylalanine; DHPR, dihydropteridine reductase activity; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; GTPCH1, GTP-cyclohydrolase I deficiency; PTPS, 6-pyruvyl-tetrahydropterin synthase deficiency; PCD, pterin-4α-carbinolamine dehydratase deficiency; DHPR, dihydropteridine reductase (DHPR) deficiency; SR, sepiapterin reductase deficiency

Presentations of Glucose Transporter Deficiency

- Microcephaly, MR, ataxia,
- Dystonic choreoathetosis, exercise induced dyskinesia
- Neonatal Seizures
- Infantile myoclonic seizures or infantile spasms
- Early-onset absence
- Myoclonic absence
- Lennox-Gastaut syndrome
- Early onset JME at times with TV screen "attraction"

Presentations of GLUT1 Deficiency New Insights

• Myoclonic epilepsy unresponsive to eight anticonvulsants. Oral steroid treatment achieved dramatic seizure control

• Alternating Hemiplegia of Childhood (only episodes of hemiplegia and delay with improvement in sleep and delay, no dystonia reported)

Development Delay, Epilepsy, and Neonatal Diabetes (DEND)

- Normally with increased sugar KATP normally closes when the ATP/ADP ratio rises, due to increased blood glucose. Thus, K+ remains intracellular, the cell depolarizes releasing insulin through Ca++.  

- Mutations make the channel less sensitive to this inhibition.
- Therapy with sulfonylureas restores channel susceptibility to inhibition

Hyperinsulinism-Hyperammonemonia Syndrome

- **Gain of function mutations** in the mitochondrial enzyme glutamate dehydrogenase, this increases ATP and inhibition of KATP
- **Symptoms:** Generalized seizures, especially absence-type seizures, in the absence of hypoglycemia.
- **Therapy:** KATP channel agonist diazoxide.

Guanidinoacetate-Methyltransferase Deficiency

- **Presentation:** Creatine disorders initially present as febrile, tonic, or tonic-clonic seizures with drop attacks and myoclonic or generalized seizures are the most frequent. Absence, focal seizures, can also occur.
- **Also:** We reported two sibs one with Lennox-Gastaut syndrome. The second had late onset West syndrome.

Alternating Hemiplegia of Childhood

• Caused by ATP1A3 mutations
• Presents with abnormal eye movements, dystonia, hemiplegia, seizures and delay
• Flunarizine helps

AHC and Neonatal Status

• Neonatal seizures: 4/9 cases
• Seizure types: tonic, myoclonic, clonic, cyanosis and apnea
  repeated episodes of status with delayed development
• MRI:
  cerebral cerebellar and hippocampal atrophy

Saito et al., Epilepsy Research 2010: 90; 248-258
Other Treatable Etiologies

- **Coenzyme Q deficiency**: of various causes has been associated with and IS and EIME at times with CFC syndrome, nephrotic syndrome and cardiomyopathy, but replacement therapy has not consistently helped.

- **Serine synthesis Defects**: Can present with neonatal seizures and later delay and microcephaly, therapy with L-serine (500 mg/kg/d, and glycine 200 mg/kg/d has been effective.

Outline

• Vitamin Responsive Disorders
  • Other Disorders
  • Clinical Approach and Utility
Clinical Approach

• **Things are not what they seem:** be familiar with the spectrum of presentations typical & atypical.

• **Keep it simple:**
  
  – Screen for inborn errors of metabolism and vitamin responsive entities that you do not want to miss
  
  – Target specific genes sequencing to the disorder you are suspecting the most
  
  – If there are none then resort to gene panel or whole exome sequencing
Workup Targeted to Ruling Out Amenably Treatable Conditions

- **Blood and Urine:** Amino acids, Organic acids, Acyl carnitine profile, carnitine free and total, lactate, pyruvate, ammonia, biotinidase, pipecolic acid, creatine, guanidino acetic acid, alpha amino adipic acid semialdehyde, MRS for creatine peak,

- **CSF:** amino acids, lactate ammonia, routines, neurotransmitter studies, Pyridoxal 5’-phosphate, 5-methyltetrahydrofolate

- **Gene Testing:** Targeted gene testing, or panels, or exome sequencing

Predictors for Positive Genetic Testing Results in Pediatric Drug Resistant Epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptic Encephalopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Present</td>
<td>89% (8)</td>
<td>11% (1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Present</td>
<td>14% (2)</td>
<td>86% (14)</td>
<td></td>
</tr>
<tr>
<td>Seizure Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>75% (6)</td>
<td>25% (2)</td>
<td>0.028</td>
</tr>
<tr>
<td>Generalized</td>
<td>24% (4)</td>
<td>76% (13)</td>
<td></td>
</tr>
</tbody>
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Retrospective study in select population in a tertiary care center, Ream and Mikati AES meeting Poster 3.278 Washington DC Dec 9, 2013.
## Diagnostic Yield of Genetic Testing
### (Retrospective Study in Select Population)

<table>
<thead>
<tr>
<th>Test</th>
<th>% of patients with at least one positive genetic test result (# positive/ # tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exome sequencing</td>
<td>83.3% (5/6)</td>
</tr>
<tr>
<td>Epilepsy gene panels</td>
<td>46% (6/13)</td>
</tr>
<tr>
<td>Single gene sequencing</td>
<td>26.7% (4/15)</td>
</tr>
<tr>
<td>Microarray</td>
<td>16.7% (2/12)</td>
</tr>
<tr>
<td>Karyotype</td>
<td>14.3% (1/7)</td>
</tr>
</tbody>
</table>

Retrospective study in select population in a tertiary care center, Ream and Mikati AES meeting Poster 3.278 Washington DC Dec 9, 2013.
Utility of Genetic Testing and Novel Presentations and Therapy

- Mutations influencing therapy: 27.6% (8/29).
- VUS variants of unknown significance: 34.5% (10/29)
- Unexpected mutations: 20.7% (6/29)

- IS, CC agenesis: GLUT1 (NL CSF gluc)
- PME: SCN1A from dad, de novo EFHC1
- IS: WDR45 (NBIA)
- IS hemimegalencephaly: PTEN gene mutation

CONCLUSIONS

Manifestations of Infantile EIEE

• Vitamin responsive disorders (Biotin, Thiamine, Folinic acid, B6 and P5P) have “classical” presentations and a range of manifestations including abnormal MRIs

• Other treatable genetic causes also have a range of presentations including brain malformations

• A systematic approach based on the above knowledge allows for successful diagnosis and early therapy of the above disorders.
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