CNS Symposium on The New Chapter of Neonatal-Onset Epilepsies: Metabolic

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When to Suspect a Metabolic Epilepsy

- Onset during neonatorum, infancy, or early childhood
- Typical clinical presentation: newborn with poor feeding, hypotonia, lethargy, respiratory distress, or lactic acidosis
- Myoclonic seizures
- EEG: burst-suppression, hypsarrhythmia
- Family history of metabolic disorder
- Poor response to traditional antiseizure Rx
4 day old: ↓ feeding, crying, alternating flaccidity/opisthotonus
Maple Syrup Urine Disease: Branched Chain Amino Acid (BCAA) Pathways:

- Leucine (LEU)
  - 2-oxoisocaproic acid
  - Isovaleryl CoA

- Isoleucine (ILE)
  - 2-oxo-3-methylvaleric acid
  - 2-methylbutyryl CoA

- Valine (VAL)
  - 2-oxoisovaleric acid
  - Isobutyryl CoA

**Series of 3 Reactions**

**Series of 3 Reactions**

**Series of 5 Reactions**

- 3-OH-3-methylglutaryl-CoA
- Acetoacetate
- Acetyl CoA
- 2-methyl-3-oxobutyryl-CoA
- Methylmalonic semialdehyde
- Propionyl-CoA

Branched-chain oxoacid dehydrogenase multienzyme complex
# EEG in Inherited Metabolic Epilepsies

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Disorder</th>
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<tbody>
<tr>
<td>Comblike rhythm</td>
<td>Maple syrup urine disease, propionic acidemia</td>
</tr>
<tr>
<td>Fast central spikes</td>
<td>Tay Sachs disease, biotinidase deficiency</td>
</tr>
<tr>
<td>RHADS</td>
<td>Alpers/POLG mutations</td>
</tr>
<tr>
<td>Rhythmic vertex-positive spikes</td>
<td>Sialidosis (type I)</td>
</tr>
<tr>
<td>Vanishing electroencephalogram</td>
<td>Infantile NCL (early infantile/type I/Haltia-Santavouri, locus 1p32, mutation in the palmitoyl-protein thiosterase gene)</td>
</tr>
<tr>
<td>High-amplitude (16-24 Hz) activity</td>
<td>Infantile neuroaxonal dystrophy</td>
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<tr>
<td>Giant SSEPs</td>
<td>Progressive myoclonic epilepsy</td>
</tr>
<tr>
<td>Marked photosensitivity</td>
<td>Progressive myoclonic epilepsy (Lafora) and NCL, particularly late infantile (type II/Bielschowsky, CLN2)</td>
</tr>
<tr>
<td>Burst suppression</td>
<td>Adrenoleukodystrophy (neonatal), citrullinemia, D-glyceric acidemia, holo-carboxylase synthetase deficiency, Leigh disease, Mb cofactor deficiency, Menkes, MTHFR deficiency, NKH, PDH/PC deficiency, propionic acidemia, sulfite oxidase deficiency</td>
</tr>
<tr>
<td>Hypsarrhythmia</td>
<td>Adrenoleukodystrophy (neonatal), CDG (type III), HHH, Menkes, neuroaxonal dystrophy, NKH, PDH, PEHO, phenylketonuria, Zellweger</td>
</tr>
<tr>
<td>Low-amplitude slowing, paroxysmal theta</td>
<td>Urea cycle defects (carbamylphosphate synthetase, OTC, argininosuccinate synthetase)</td>
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# Neonatal Onset Metabolic Epilepsies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>ALDH7A1 (B6); PNPO (P5P); Folinic acid Dependency</td>
<td>B6 100 mg IV, 5-15 mg/kg/D; P5P 10-40 mg/kg/D; folinic 3-5 mg/kg/D</td>
</tr>
<tr>
<td>Biotinidase/holocarboxylase deficiency</td>
<td>Biotin 10 mg/D</td>
</tr>
<tr>
<td>DEND (neonatal diabetes)</td>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>GABA-transaminase deficiency</td>
<td>Flumazenil?</td>
</tr>
<tr>
<td>Glucose transporter-1 deficiency</td>
<td>Ketogenic diet</td>
</tr>
<tr>
<td>Glycine encephalopathy</td>
<td>Na benzoate, dextromethorphan</td>
</tr>
<tr>
<td>HI/HA (hyper-insulinism/-ammonemia)</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>Menkes disease</td>
<td>Cu histidine (subcut)</td>
</tr>
<tr>
<td>MOCOF, sulfite oxidase deficiency</td>
<td>cPMP (Mb cofactor precursor), type A</td>
</tr>
<tr>
<td>Organic acidurias (PA, MMA, IVA)</td>
<td>Dietary; dispose of toxins, e.g. NH3</td>
</tr>
<tr>
<td>Peroxisomal disorders</td>
<td>Dietary, adjunctive compounds</td>
</tr>
<tr>
<td>Serine biosynthesis defects</td>
<td>L-ser 200-600 mg/kg/D</td>
</tr>
<tr>
<td>Urea cycle disorders</td>
<td>Dietary, adjunctive compounds</td>
</tr>
</tbody>
</table>
Acute but Reversible Severe Epileptic Encephalopathies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
Acute but Reversible Severe Epileptic Encephalopathies

• Vitamin Responsive Disorders
  – Pyridoxine
  – Pyridoxal-5-phosphate
  – Folinic acid
  – Biotin

• Transportopathies
• Amino and Organic Acid Disorders
• Mitochondrial Disorders
• Urea Cycle Disorders
• Neurotransmitter Disorders
• Disorders of Glucose Homeostasis
Neonatal Seizures

- FT NBN 3220 gms
- Abnormal eye movements, grunting 12 hrs
- EEG: episodic suppression, bilateral sharp waves
- Rx phenobarbital, levetiracetam, pyridoxine: seizure-free X 6 wks
- Hospitalized at 3.5 months for stiffening, Rx topiramate
- Mycolonic & tonic-clonic seizures; steroids ineffective
• Pyridoxal-5-phosphate stopped seizures with first dose. Breakthrough events as dose becomes due.
• CSF levels for P5P = 23 (23-64), ↑ thr; extra peak (suspected pyridoxine phosphate).
• PNPO sequencing: homozygous mutation, conserved area, gly>arg.

PNPO Deficiency

• Clinical Triad
  – Rotatory eye movements, hyperexcitability, hypersalivation (I Tein 2015)

• CSF Profile
  – Elevated glycine, threonine
  – Depressed [P5P]
EEG of patient with PNPO deficiency, age 3.5 months, showing paroxysms of diffuse spike-wave discharges accompanied by multifocal myoclonic and erratic movements.
PYRIDOXINE DEPENDENCY: REPORT OF A CASE OF INTRACTABLE CONVULSIONS IN AN INFANT CONTROLLED BY PYRIDOXINE

By Andrew D. Hunt, Jr., M.D.,* Joseph Stokes, Jr., M.D., Wallace W. McCrory, M.D., and H. H. Stroud, M.D.

Philadelphia

The importance of pyridoxine in animal and human nutrition has been a subject of wide interest since its original description as a B factor by György in 1934. Unlike the majority of vitamins, however, no pathologic condition in humans has been described which occurred spontaneously and was corrected solely by the administration of pyridoxine. The authors recently observed an infant with a severe convulsive disorder who responded in an extraordinary manner to regular administration of pyridoxine. This phenomenon was thought to be unique and to warrant the following case report.

CASE REPORT

A. M., a female infant, was admitted to The Children's Hospital of Philadelphia at the age of 13 days because of constant and intractable convulsions. Mrs. M.'s first pregnancy had been normal, devoid of illness or significant nausea and vomiting. The second pregnancy, however, was accompanied by severe nausea and vomiting which was treated with injections of pyridoxine and thiamine during the 1st 4 mo. of gestation.

Pregnancy with the patient also resulted in severe nausea and vomiting, sufficiently so to require hospitalization on 1 or 2 occasions for intravenous fluids. During the second, third, fourth and fifth months of this pregnancy she was given, 3 to 4 times weekly, an intramuscular injection consisting of pyridoxine HCl 50 mg., and thiamine HCl, 50 mg. No adverse reactions were noted during this therapy.

Labor had a spontaneous onset, occurred at term, and was of 4 hr.'s duration. No difficulties were encountered during delivery, birth weight was 3.2 kg., respirations began spontaneously, and the baby's color was considered good. However, 3 hr. after birth, generalized twitching accompanied by shrill cries made its...
Antiquitin (AASDH) deficiency in Pyridoxine dependent epilepsy

When AASDH (antiquitin) activity is deficient, pipecolic acid and P6C both accumulate. P6C sequesters PLP, the biologically active form of pyridoxine.

\[ \text{Lysine} \rightarrow \text{Pipecolic acid} \rightarrow \alpha\text{-Aminodipic-semialdehyde} \rightarrow \alpha\text{-Aminoadipate} \]

\[ \text{Pyridoxine} \rightarrow \text{PLP} \rightarrow \text{P6C} \]

**AASDH** = alpha-Aminodipic-semialdehyde Dehydrogenase (*antiquitin*); **P6C** = delta-Piperideine-6-carboxylate; **PNPO** = Pyridox(am)ine oxidase; **PLP** = Pyridoxal-5-phosphate
Folinic acid responsive seizures


• Prompt response 2.5-5 mg twice daily

• Crossover between pyridoxine and folinic acid responsiveness in same individuals (Gallagher et al: Folinic acid responsive seizures are identical to pyridoxine-dependent epilepsy. Ann Neurol 2009)
B6 or P5P for Neonatal Epilepsy

The distinction just got murkier
Pearl and Gospe 2014 Neurology

• Plecko et al 2014 Neurology
  – 31 patients w/B6 responsive neonatal sz’s
  – NI PDE biomarkers & ALDH7A1 sequencing
  – 11 patients w/PNPO mutations
  – P5P led to status in 2

• Mills et al 2014 Brain
  – (i) neonatal onset seizures, P5P responsive
  – (ii) infantile spasms (5 mos), P5P responsive
  – (iii) infantile onset (< 3 mos), B6 responsive
Lessons Learned in B6/P5P Dependencies

- Exclusive PLP responsiveness in PNPO mutations is wrong.
- Sequential testing of B6, PLP must replace PLP Rx for both.
- PNPO mutations relevant even if B6 responsive.
- Trials of B6 and P5P indicated in AED resistant neonatal seizures (even if birth asphyxia suggested clinically)
- PNPO deficiency may be more common than antiquitin deficiency
- New approaches: lysine restricted diet, glycine and arginine supplementation (competitive inhibition of lys transport)
Pyridoxine Responsive Epilepsies

1. ALDH7A1/antiquitin deficiency
2. PNPO deficiency
3. Hyperphosphatasia with Intellectual deficiency (Mabry syndrome)
   - Glycosylphosphatidylinositol deficiency
   - Impairment of alkaline phosphatase mediated cleavage of P5P
4. Hyperprolinemia type II (ALDH4A1)
   - 1-pyrroline-5-carboxylate dehydrogenase def
   - Pyrroline-5-carboxylate accumulates
Approach to Intractable Neonatal Seizures
Suspect for Pyridoxine Related Dependency

Diagnostics:
• Blood, Urine for AASA, pipecolic acid
• DNA for ALDH7A1 or PNPO molecular analysis

Treatment:
• B6 100 mg IV bolus (5-10 mins) with EEG + cardiorespiratory monitoring.
• If no response, repeat 100 mg IV B6 bolus.
• In responders, observe as inpatient a minimum of 48 hours.

• While biomarkers are pending, consider oral/enteral B6 15-30 mg/kg/day divided BID.
• Begin P5P 30-50 mg/kg/day divided 4-6 X/day when available X 3-5 days.
• Folinic acid 3-5 mg/kg/D divided BID X 3-5 days.
Biotinidase Deficiency

- Developmental delay
- Hypotonia
- Seizures
- Ataxia
- Alopecia, perioral rash
- Episodic metabolic acidosis
- Hearing loss
- Vision loss, optic atrophy
- Lactic and propionic acidemia
Biotinidase Pathway

Dietary protein-bound Biotin → Biocytin → Free Biotin

Biotin

Holocarboxylase synthetase

Apocarboxylases

Dietary Free Biotin
Patients with Biotinidase Deficiency

Secondary biotinidase deficiency (beyond multiple carboxylases)

1. Dietary deficiency (vegan diets)
2. Malabsorption
3. Hemodialysis
4. Parenteral nutrition
5. Drugs, e.g. valproic acid

Suggested if increased plasma lactate, NH3, or 3-OH-isovaleric on urine organic acids
Treatment of Biotinidase Deficiency

• Gratifying response to biotin 10 mg/day.
• Vision and sensorineural hearing loss, once established, persist.
Clinical Landmines: Biotinidase Deficiency

1. Misdiagnosed as “atypical” or “childhood” multiple sclerosis. Patients may present in *adolescence with spastic paraparesis*. Dermatologic manifestations misdiagnosed as acrodermatitis enteropathica or anhidrotic ectodermal dysplasia.

2. Seizures (generalized, myoclonic, or infantile spasms) occur in the majority of patients and may be the *only obvious symptom*. Testing for biotinidase deficiency is warranted in any patient with unexplained seizures.
Acute but Reversible Severe Epileptic Encephalopathies

- Vitamin Responsive Disorders
- Transportopathies
  - Glucose
  - Folate, thiamine, riboflavin, manganese – infantile onset and later
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
GLUT1 Deficiency

• 3 phenotypes
  – 1. Classic: neonatal seizures, microcephaly
  – 2. Delay, dysarthria, dystonia
  – 3. Choreoathetosis, dystonia, paroxysmal exertional dyskinesias

• CSF glc < 40-60; CSF/serum < 0.4 X 3

• MRI: T2 hyperintensities, subcort U fibers

• SLC2A1 mutations in 10% early onset absence, and in MAE of Doose

• PBS, DZP, Cl hydrate, VPA: inhibit GLUT
Secondary causes of Hypoglycorrhachia

• Meningitis (esp bacterial, TB)
• Status epilepticus
• Mitochondrial disorders
• Systemic hypoglycemia
• Subarachnoid hemorrhage
• Meningeal carcinomatosis
Differential Diagnosis of CSF 5MTHF

- 1. FOLR1 mutations, blocking/binding Abs
- 2. 5,10-MTHFR deficiency
- 3. 3-phosphoglycerate dehydrogenase def.
- 4. DHFR/DHPR def. (biotinidase synthesis/recycling)
- 5. Hereditary folate malabsorption
- 6. Rett, Aicardi-Goutieres, mitochondrial (KSS)
- 7. Drugs, e.g. valproate
- 8. Deficiency dietary intake
- 9. Proton-coupled folate transporter 1 (PCFT1) deficiency
- 10. KCNH1 mutations
Acute but Reversible Severe Epileptic Encephalopathies

• Vitamin Responsive Disorders
• Transportopathies
• **Amino and Organic Acid Disorders**
  – Propionic, methylmalonic, isovaleric
  – Serine synthesis
  – Creatine synthesis
  – Many require rapid recognition to reduce ammonia, ICP, dietary restrictions. Assess toxic neonate with negative sepsis evaluation for lactic acid & NH3.

• Mitochondrial Disorders
• Urea Cycle Disorders
• Neurotransmitter Disorders
• Disorders of Glucose Homeostasis
Congenital microcephaly, neonatal seizures, infantile spasms

Glucose $\rightarrow$ 3-Phosphoglycerate $\rightarrow$ Pyruvate

3-Phosphohydroxypyruvate

3-Phosphoserine

L-Serine

Glycine

THF

5-MTHF

5,10 MTHF

Methionine

Homocysteine
Serine Biosynthesis Disorder

- Low CSF and (fasting) plasma serine
- Treatable with serine supplementation (400-600 mg/kg/day) and glycine (200-300 mg/kg/day).
- Normal outcome with pre- and post-natal Rx
Creatine Synthesis/Transport

Check plasma/urine creatine and GAA.

AGAT: Arginine:Glycine Aminidotransferase
GAMT: Guanidinoacetate N-Methyltransferase
Metabolic Disorders of Creatine

• First described in 1994: GAMT deficiency.
• GAA level: ↑ GAMT; ↓ AGAT; nl transporter defect
• Rx: creatine (GAMT, AGAT deficiencies); arginine restriction, ornithine supplementation (GAMT)
• Normalization of outcome in presymptomatic neonatal intervention (Schulze, Hoffmann, Bachert et al. Neurology 2006)
## Clinical Symptoms in Disorders of Creatine Metabolism

<table>
<thead>
<tr>
<th>Condition</th>
<th>GAMT</th>
<th>AGAT</th>
<th>Creatine Transporter 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced somatic growth</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Early developmental delay</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neurologic regression</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Intellectual deficiency</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Autistic behavior</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Hypotonia</td>
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<td>X</td>
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<tr>
<td>Epilepsy</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Movement disorder</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>MRI: abnormal pallidal signal</td>
<td>X</td>
<td></td>
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</tbody>
</table>
New hope for Mb cofactor deficiency

- Mb dependent enzymes
  - Sulfite oxidase, xanthine oxidase, nitrate reductase, nitrogenases
  - Type A: lack cyclic pyranopterin monophosphate (cPMP)
- Early presentation: EIEE
- Later presentation: GDD
- Laboratory: decreased uric acid, + urine sulfites, elevated U S-sulfocysteine, xanthine, hypoxanthine
Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study

**Summary**

Background: Molybdenum cofactor deficiency (MoCD) is characterized by early, rapidly progressive postnatal encephalopathy and intractable seizures, leading to severe disability and early death. Previous treatment attempts have been unsuccessful. After a pioneering single treatment we now report the outcome of the complete first cohort of patients receiving substitution treatment with cyclic pyranopterin monophosphate (cPMP), a biosynthetic precursor of the cofactor.

Methods: In this observational prospective cohort study, newborn babies with clinical and biochemical evidence of MoCD were admitted to a compassionate-use programme at the request of their treating physicians. Intravenous cPMP (50–120 μg/kg per day) was started in neonates diagnosed with MoCD (type A and type B) following a standardized protocol. We prospectively monitored safety and efficacy in all patients exposed to cPMP.

Findings: Between June 6, 2006, and Jan 9, 2013, intravenous cPMP was started in 36 neonates diagnosed with MoCD (11 type A and five type B) and continued in eight type A patients for up to 5 years. We observed no drug-related serious adverse events after more than 600 doses. The disease biomarker urinary Sulfophosphomolybdic acid and urate returned to almost normal concentrations in all type A patients within 2 days, and remained normal for up to 5 years on continued cPMP substitution. Eight patients with type A disease rapidly improved under treatment and were discharged home. Five patients treated early remained seizure-free and showed near-normal long-term development. We detected no biochemical or clinical response in patients with type B disease.

Interpretation: cPMP substitution is the first effective therapy for patients with MoCD type A and has a favorable safety profile. Restoration of molybdopterin cofactor-dependent enzyme activities results in a greatly improved neurodevelopmental outcome when started sufficiently early. The possibility of MoCD type A needs to be urgently explored in every encephalopathic neonate to avoid any delay in appropriate cPMP substitution, and to maximize treatment benefit.

**Funding**

German Ministry of Education and Research, Orphanet, European Foundation for the Treatment of Childhood Disorders.

**Introduction**

MoCD usually manifests during the first few postnatal days with exaggerated startle reactions, abnormities in muscle tone, lethargy, intractable seizures, and autonomic dysfunctions. At the onset of classical symptoms brain imaging reveals global white matter and deep grey matter involvement, followed by rapidly evolving widespread subcortical necrosis. Multisystem lesions appear within weeks, with subsequent brain atrophy and secondary microcystic lesions. Some patients display developmental anomalies, such as craniofacial dysmorphia, microcephaly, skeletal bowing, and hypoplastic nails.
Acute but Reversible Severe Epileptic Encephalopathies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
  - Pyruvate dehydrogenase deficiency (Rx – ketogenic diet)
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
Acute but Reversible Severe Epileptic Encephalopathies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
Urea Cycle Disorders

- Extended tandem MS will detect two: ASS, ASL, sometimes arginase def
- But not directly detect OTC, CPSI, NAGS
- Consider hyperammonemia in sick neonate, especially breastfed infant deteriorating after starting to feed and ingest protein
- Immediately cease protein intake and use NH3 lowering Rx
Acute but Reversible Severe Epileptic Encephalopathies

• Vitamin Responsive Disorders
• Transportopathies
• Amino and Organic Acid Disorders
• Mitochondrial Disorders
• Urea Cycle Disorders
• Neurotransmitter Disorders
• Disorders of Glucose Homeostasis
Pathways of biogenic monoamine neurotransmitters. 5-HTP = 5-hydroxytryptophan; 5-HIAA = 5-hydroxyindoleacetic acid; GTP = guanosine triphosphate; BH4 = tetrahydrobiopterin; BH2 = quinonoid dihydrobiopterin; L-DOPA = levodopa; HVA = homovanillic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol; VMA = vanillylmandelic acid. {1} tryptophan hydroxylase; {2} tyrosine hydroxylase; {3} aromatic-L-amino acid decarboxylase; {4} monoamine oxidase; {5} monoamine oxidase, aldehyde dehydrogenase, catechol-O-methyltransferase; {6} dopamine β-hydroxylase; {7} phenylethanolamineN-methyltransferase; {8} GTP-cyclohydroxylase I
Tetrahydrobiopterin (BH₄) Metabolism

GTP → Dihydroneopterin triphosphate → 6-pyruvoyl-tetrahydropterin → Biopterin → BH₄

- GTP = Guanine triphosphate
- GTPCH = GTP Cyclohydrolase I
- PTPS = 6-pyruvoyl-tetrahydropterin synthase
- SR = Sepiapterin Reductase
- BH₄ = Tetrahydrobiopterin
- DHPR = Dihydropterin Reductase
- Trp OH’ase = Tryptophan Hydroxylase
- TH = Tyrosine Hydroxylase
- PAH = Phenylalanine Hydroxylase
- 5-HTP = 5-Hydroxytryptophan
- PCD = Pterin-carbinolamine Reductase
- q-BH₂ = q-Dihydrobiopterin
GTP: Guanine triphosphate; GTPCH: GTP Cyclohydrolase I; DNTP: Dihydrobiopterin triphosphate; PTPS: 6-Pyruvoyl-tetrahydropterin synthase; 6-PTP: 6-Pyruvoyl-tetrahydropterin; SR: Sepiapterin reductase; BH₄: Tetrahydrobiopterin; DHPR: Dihyropterin reductase; DHFR: Dihydrofolate reductase; BH₂: quinonoid dihydrobiopterin; PCD: pterin-4α-carbinolamine dehydratase.
7 yo girl w/DHPR deficiency, Rx delayed to 3 years of age
EEG at 21 months (left) versus 26 months (right) on flumazenil trial, Dx: GABA transaminase deficiency (HFF 70 Hz, LFF 1 Hz, sens 10 mcV/mm) (CNS Mtg 2016 Poster)
Acute but Reversible Severe Epileptic Encephalopathies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
  - Neonatal diabetes
  - Congenital hyperinsulinism
DEND

- Developmental Delay
- Epilepsy
- Neonatal Diabetes

Metabolic Regulation of $K_{ATP}$ Channels and DEND Syndrome

A) Normal regulation under low plasma glucose, low metabolism conditions

Cellular Metabolism Low
↓ATP:ADP
↑MgADP

Membrane potential: -70mV
(Hyperpolarized)

Voltage gated

K Channel sensitive to ATP:ADP

Insulin

SURL

$K_{ATP}$ Kir6.2 OPEN
Metabolic Regulation of $K_{ATP}$ Channels and DEND Syndrome

B) Normal regulation under high plasma glucose, high metabolism conditions

Glucose → Metabolism → $K_{ATP}$ Channel sensitive to ATP:ADP

$K_{ATP}$ Kir6.2 CLOSED → ATP:ADP ↑, MgADP ↓ → K+ "-" → Membrane Depolarized → Ca²⁺ "+" → Insulin release → Insulin → Voltage gated Ca²⁺ OPEN
Metabolic Regulation of $K_{ATP}$ Channels and DEND Syndrome

C) Abnormal K channel sensitivity, DEND Syndrome under high glucose, high metabolism conditions

- Glucose
- Metabolism
- $K_{ATP}$
- Insulin
- $Ca^{2+}$
- Voltage gated
- K Channel insensitive to ATP:ADP, remains open
- Membrane potential: -70mV (Hyperpolarized)
- ATP:ADP
- MgADP

No insulin release
DEND Syndrome: Treatable with oral hypoglycemic agents (NOT insulin)

• Most cases due to KCNJ11 mutations
• Channels normally close with hyperglycemia, promoting depolarization and insulin release
• Sulfonylurea binds to receptors, promoting closure and physiologic insulin release
• Improved neurological outcomes with sulfonylureas
13 yr old boy with GTCS & absence, learning disabilities, generalized spike-wave

- Neonatal seizures
- Hypoglycemia
- Frontal hemorrhagic infarction
- Dx “noccidioblastosis”
- Pancreatectomy refused
- Worsened pre-prandially and post-protein meals
Insulin Secretion Pathway and Mechanism of Hyperinsulinism-Hyperammonenemia Syndrome in Pancreatic β–Islet Cells

- GTP
- Leucine
- Glutamate
- a-Ketoglutarate
- NH₃
- TCA Cycle
- K⁺ ATP Channel Closure (Membrane Depolarization)
- ↑ ATP:ADP
- ↑ Insulin Release
Hyperinsulinism-Hyperammonemonia (HI-HA)

- Congenital hyperinsulinism
- Activating mutations GLUD1 (glutamate dehydrogenase)
- Recurrent symptomatic hypoglycemia, with fasting or high protein meal
- Epilepsy, learning, behavior disorders
- Rx protein restriction, AEDs, and diazoxide (hyperglycemic which activates, i.e. opens, K channels, inhibiting insulin release).

NEONATAL/EARLY ONSET EPILEPTIC ENCEPHALOPATHY

History, Family History, Examination, EEG

• MRI (3T) with MRS

MRI normal or non-specific

Malformation of cortical development
• Malformation specific genetic +/- metabolic testing

Vascular or traumatic etiology
• Targeted evaluation

Dysmorphism, systemic findings, congenital malformations, or clinical features of a specific syndrome

• Syndrome specific molecular testing
• Chromosomal microarray
• Whole exome sequencing

Laboratory testing (LP done 4 hr postprandial):
Electrolytes, glucose, ammonia, lactic acid, plasma amino acids, creatine/GAA, pipecolic acid, alpha aminoacidipic semialdehyde, copper/ ceruloplasmin, homocysteine, biotinidase
Urine organic acids, AASA
CSF cell count, glucose, protein, cultures, amino acids, lactate, pyruvate, neurotransmitters, P5P, 5-MTHFR
Consider U sulfites; VLCFAs; N&O glycosylation panel;
Blood, urine, or CSF metabolomics panel

Genetic testing:
• Epilepsy gene/ROI panel
• Chromosomal microarray
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