Diagnosing Genetic Epilepsies – Impact on Treatment
Cleveland Clinic Foundation
Epilepsy Course 2020
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OBJECTIVES

1. Explore the genetic and metabolic basis of epilepsies.
2. Decide when to order genetic testing.
3. Identify cardinal signs of inherited metabolic epilepsies.
4. Intervene with targeted therapy when available in genetic-metabolic epilepsies.
Historical Underpinnings of Epilepsy

• But this disease seems to me to be no more divine than others; but it has its nature such as other diseases have, and a cause whence it originates, and its nature and cause are divine only just as much as all others are, and it is curable no less than the others...Its origin is hereditary, like that of other diseases.
Historical Underpinnings of Epilepsy

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*On the Sacred Disease*

Hippocrates

400 BCE
Epilepsy Genetics: Milestones

- Familial epilepsy
  - Lennox, twin studies
- “Idiopathic epilepsy”
  - Presumed genetic
- Mapping of the Human Genome
  - 2001
- Personalized, Targeted Therapies
Why Do Genetic Testing?

• 1. Diagnostic Certainty
  – End the odyssey.
  – Aid in prognosis.

• 2. Genetic Counseling

• 3. Impact on Treatment
Impact on Treatment? YES.

• Loss of function – haploinsufficiency
  – SCN1A – Dravet syndrome (avoid Na blockers)
  – SLC2A1 – GLUT1 deficiency (ketogenic diet, carnitine, alpha-lipoic acid)

• Gain of function
  – SCN8A (respond to Na channel blockers)
  – KCNT1 (migratory focal epilepsy of infancy)
Who To Test?

- “Epilepsy Plus”
  - Dysmorphism, cognitive deficit, autism
- CMA
  - Yield of 1.5-5%  (Olson et al, Ann Neuro 2014; Lindy et al, Epilepsia 2018)
- Panel or exome sequencing
  - Yield of 15-50%  (Helbig et al, Genet Med 2016; Lindy et al, Epilepsia 2018)
What about the “Genetic Generalized Epilepsies”?

- $\frac{1}{4}$ of all epilepsies
- Generalized spike/wave, normal imaging, normal cognition
- Typical absence, myoclonic, GTCS
- Genetic contribution is suspected
- Monozygotic vs Dizygotic concordance is 76% vs 33% (strongly but not exclusively genetic)
- 8% siblings affected
- Polygenic inheritance presumed
Case Study 1

- 14 yo girl with JME
- FH positive for epilepsy (maternal side)
- Does genetic testing add?
  - If regression occurs, consider other dx’es.
  - Pharmacogenetics may add in Rx choice.
  - Not especially helpful in the more common epilepsies.
Study 2

• A 6 month old boy with infantile spasms, normal MRI.

• A pathogenic variant in an “epilepsy gene” would allay further studies and potentially repeated imaging.

• Possible impact on Rx choice.
Categories of Inherited Metabolic Epilepsies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
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 antiepileptic drug
Treatable Metabolic Epilepsies

Specific Disorders

- Vitamin Responsive Disorders
  - Pyridoxine, P5P, Folinic acid, Biotin
- Transportopathies
  - GLUT1, Cerebral Folate Deficiency, Thiamine Transporter
- Amino and Organic Acid Disorders
  - MSUD, propionic, isovaleric, cobalamin C
- Lysosomal Storage Diseases
  - LINCL/CLN2
- Mitochondrial Disorders
  - PDHC deficiency
- Purine Synthesis Disorders
  - MoCo deficiency type A
- Urea Cycle Disorders
  - OTC deficiency
- Neurotransmitter Disorders
  - BH4, GABA-transaminase
- Disorders of Glucose Homeostasis
  - DEND, HI/HA
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]
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 twitches accompanied by shrill cries made its

Antiquitin (AASDH) deficiency in Pyridoxine dependent epilepsy

Lysine → Pipecolic acid → α-Aminodipic-semialdehyde → AASDH → α-Aminoadipate

Pyridoxine → PLP → P6C

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

AASDH = alpha-Aminodipic-semialdehyde Dehydrogenase (antiquitin); P6C = delta-Piperideine-6-carboxylate; PNPO = Pyridox(am)ine oxidase; PLP = Pyridoxal-5-phosphate
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 100-500 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 Pathway

- Dietary protein-bound Biotin
- Biocytin
- Free Biotin
- Biotin
- Holocarboxylases
- Apocarboxylases
- Holocarboxylase synthetase

The pathway begins with dietary protein-bound biotin, which is converted to biocytin. Biotinidase then converts biocytin to free biotin, which is then used by holocarboxylases. Apocarboxylases are synthesized from free biotin, completing the pathway.
Biotinidase Deficiency: Phenotypic Components

• Developmental delay
• Hypotonia
• Seizures
• Ataxia
• Alopecia, perioral rash
• Episodic metabolic acidosis
• Hearing loss
• Vision loss, optic atrophy
• Lactic and propionic acidemia
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
Treatment of Biotinidase Deficiency

• Gratifying response to biotin 10 mg/day.
• Visual 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
- Lysosomal Storage Diseases
- Mitochondrial Disorders
- Purine Metabolism Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
GLUT1 Deficiency

• 3 “phenotypes” appear to be an ontogenic spectrum
  – 1. “Classic”: neonatal seizures, microcephaly
  – 2. Infancy: Delay, dysarthria, dystonia
  – 3. Later: 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
GLUT1 DS: Treatment

- Ketogenic diet, carnitine (to augment diet)
- Alpha lipoic acid
  - augments GLUT1 function
- Avoid PBS, DZP, Cl hydrate, VPA
  - inhibit GLUT1 function
Secondary causes of Hypoglycorrhachia

- Meningitis (esp bacterial, TB)
- Status epilepticus
- Mitochondrial disorders
- Systemic hypoglycemia
- Subarachnoid hemorrhage
- Meningeal carcinomatosis
FRI Mediated Endocytosis Across the BBB

Vascular endothelial barrier
RFCl
RFCl
RF2
FR1
F
RFC
F
Blood-CNS barrier
Neuronal cells
F consumption
catabolism
DHF
DHFR
F
Vascular endothelial barrier
RFCl
RFCl
RF2
FR1
F
RFC
F
Diet
F
Intestinal barrier
RBC

Manifestations: Cerebral Folate Deficiency

- Infantile onset (4-6 months)
  - Irritability
  - Decelerating head growth
  - Seizures
  - Psychomotor retardation
  - Cerebellar ataxia
  - Pyramidal tract signs
  - Ballismus, choreoathetosis

- After three years of age:
  - Optic atrophy
  - Cortical blindness
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. (BH4 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
Thiamine Transporter-2 Deficiency

- Formerly biotin responsive basal ganglia disease
- SLC19A3 mutations
- Acute encephalopathy, dystonia, seizures
  - Alfadhel et al: Biotin-responsive basal ganglia disease should be renamed biotin-thiamine-responsive basal ganglia disease. Orphanet J Rare Dis 2013.

Figure: Ortigoza-Escobar et al: Thiamine transporter-2 deficiency: outcome and treatment monitoring. Orphanet J Rare Dis 2014.
Acute but Reversible Severe Epileptic Encephalopathies

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

- Lysosomal Enzyme Disorders
- Mitochondrial Disorders
- Purine Metabolism Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
4 day old: ↓ feeding, crying, alternating flaccidity/opisthotonus
Maple Syrup Urine Disease

- Branched-chain ketoaciduria
  - Deficiency in branched-chain α-keto acid dehydrogenase (BCKD) complex
  - Accumulation of branched amino acids: leu, ile, val

valine
leucine
isoleucine
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
- Isobutryl CoA

Branched-chain oxoacid dehydrogenase multienzyme complex

SERIES OF 3 REACTIONS
- 3-OH-3-methylglutaryl-CoA
- acetoacetate
- acetyl CoA

SERIES OF 3 REACTIONS
- 2-methyl-3-oxobutyryl-CoA

SERIES OF 5 REACTIONS
- Methylmalonic semialdehyde
- propionyl-CoA
Major Phenotype

• Overwhelming illness in first days of life: lethargy to coma

• Opisthotonus

• Convulsions

• Recurrent episodes
Two patients with MSUD

From: Atlas of Metabolic Diseases 2005
Teenage girl with MSUD

From: Atlas of Metabolic Diseases 2005
Categories of Inherited Metabolic Epilepsies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Lysosomal Storage Diseases
- Mitochondrial Disorders
- Purine Metabolism Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
Neuronal Ceroid Lipofuscinoses

- 13 reported genes, 160+ mutations
- Late infantile NCL2: CLN2
- TPP1 gene
- Deficiency of tripeptidyl peptidase 1
- Onset 2-4 years
- Dementia, seizures, visual impairment
- Seizures: GTCS, atonic, astatic, myoclonic, absence, focal onset
- Action myoclonus
Interictal – CLN2

EEG courtesy of Elaine Wirrell MD, Mayo Clinic
1 Hz PPR

EEG courtesy of Elaine Wirrell MD, Mayo Clinic
3 Hz PPR

EEG courtesy of Elaine Wirrell MD, Mayo Clinic
Newly approved Treatment for CLN2/LINCL

Recombinant human TPP1
Cerliponase alfa
Rx Brineura, FDA approved 2017
Intraventricular delivery
Efficacy studied in 22 patients 3-8 years old.
Fewer declined in walking ability compared to natural history study.
Congenital microcephaly, neonatal seizures, infantile spasms

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

$\downarrow$ Dehydrogenase

3-Phosphohydroxypyruvate

$\downarrow$

3-Phosphoserine

$\downarrow$ Phosphatase

L-Serine

THF $\leftrightarrow$ 5-MTHF

Methionine $\leftrightarrow$ Homocysteine

Glycine
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>Symptom</th>
<th>GAMT</th>
<th>AGAT</th>
<th>Creatine Transporter 1</th>
</tr>
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<tbody>
<tr>
<td>Reduced somatic growth</td>
<td></td>
<td>X</td>
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<tr>
<td>Early developmental delay</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Neurologic regression</td>
<td>X</td>
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<tr>
<td>Intellectual deficiency</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Autistic behavior</td>
<td>X</td>
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<tr>
<td>Hypotonia</td>
<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>
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<tr>
<td>MRI: abnormal pallidal signal</td>
<td>X</td>
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Categories of Inherited Metabolic Epilepsies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Lysosomal Storage Diseases
- Mitochondrial Disorders
- **Purine Metabolism Disorders**
- Urea Cycle Disorders
- Neurotransmitter Disorders
- Disorders of Glucose Homeostasis
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 seizures, rapidly progressive postural-kinetic myoclonus, and intractable seizures, leading to severe disability and early death. Previous treatment attempts have been limited. 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 bioavailable precursor of the cofactor.

Methods In this observational prospective cohort study, newly diagnosed MoCD were admitted to a comprehensive-care program at the request of their treating physicians. Intravenous cPMP (80–120 μg/kg per day) was started in neonates diagnosed with MoCD type A and type B following a standardized protocol. We prospectively measured safety and efficacy in all patients exposed to cPMP.

Findings Between June 6, 2000, and Jan 1, 2013, intravenous cPMP was started in 38 neonates diagnosed with MoCD (11 type A and 27 type B) and continued in eight type A patients for up to 13 years. Of the 38 patients, 18 died, including seven on cPMP substitution. Eight patients with type A disease rapidly improved under treatment and continued to use cPMP for 3–20 years. Of the seven patients treated with type B disease, five had improved early in the treatment period and continued to use cPMP for 1–11 years. All patients treated early remain seizure-free and show some normal long-term development. We detected no biochemical or clinical response in patients with type B disease and a survival benefit of cPMP substitution.

Interpretation cPMP substitution is the first effective therapy for patients with MoCD type A and has a formidable safety profile. Restoration of molybdenum cofactor-dependent enzyme activities results in a greatly improved neurodevelopmental outcome when started sufficiently early. The possibility of MoCD type A being treatable eventually may explain in every metabolically normal neonate to avoid any delay in appropriate cPMP substitution, and to maximize treatment benefit.

Funding German Ministry of Education and Research, Orphanet, California Pharmaceuticals.

Introduction Human molybdenum cofactor deficiency (MoCD) usually manifests during the first few postnatal days with exaggerated startle reactions, seizures, ataxia, hyperreflexia, and intractable seizures, leading to neonatal death.

At the onset of clinical symptoms, brain imaging reveals global white matter and deep grey matter involvement, followed by rapidly evolving widespread subcortical and cerebellar atrophy.

Some patients display developmental abnormalities, such as learning disabilities or malformations of the cranial and facial bones.

Several patients develop abnormalities of the extrapyramidal system and dyskinesia. MLD and ALCAD phenotypes may show similar symptoms in muscle tone and deep tendon reflexes.

Seizures usually develop within the first weeks of life and are often difficult to control. Many patients have a history of hypotonia, hyporeflexia, and mild dysmorphic facial features and seizures.

Some patients have a history of progressive psychomotor retardation and severe intellectual disability. Seizures may persist into adulthood. However, in most patients, seizures tend to improve or even disappear after treatment.

Brain imaging shows diffuse areas of hypoperfusion, decreased metabolic activity, and white matter changes consistent with cerebral atrophy. Even after successful treatment, brain imaging may show persistent abnormalities.

The mainstay of treatment is neurological support, including anticonvulsants, antispasticity, and therapy directed at the underlying metabolic defects.

Recently, several centers have reported success in treating patients with MoCD type A and type B using intravenous cPMP.

Intravenous cPMP is the first effective therapy for patients with MoCD type A and has a formidable safety profile. Restoration of molybdenum cofactor-dependent enzyme activities results in a greatly improved neurodevelopmental outcome when started sufficiently early. The possibility of MoCD type A being treatable eventually may explain in every metabolically normal neonate to avoid any delay in appropriate cPMP substitution, and to maximize treatment benefit.
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
  - Na benzoate/Na phenylacetate, dialysis
- 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
Acute but Reversible Severe Epileptic Encephalopathies

- Vitamin Responsive Disorders
- Transportopathies
- Amino and Organic Acid Disorders
- Mitochondrial Disorders
- Urea Cycle Disorders
- Neurotransmitter Disorders
  - BH4, monoamine precursors, MAO-inhibitors
- Disorders of Glucose Homeostasis
Disorders of Recycling or Synthesis of BH$_4$

- Usually diagnosed due to hyper-phenylalanine on the newborn screen.

- Some of these conditions are associated with normal blood [phe].
  - Evaluation for a disorder in the BH4 pathway should be done in infants with unexplained neurologic disease.
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 → GTPCH → Dihydronopterin triphosphate → PTPS → 6-pyruvoyl-tetrahydropterin → SR → BH₄ → DHPR

Tryptophan → Trp OH’ase → TH → PAH → L-Dopa → Tyrosine → Tyrosine → PCD → q-BH₂

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.
Major Phenotype of BH₄ Disorders

- Intellectual disability
- (Myoclonic) seizures
- Muscular rigidity
- Dystonia
- Drooling
- Microcephaly
- Neuroimaging:
  - cerebral atrophy, lucency of the white matter, basal ganglia calcifications
7 yo girl w/DHPR deficiency, Rx delayed to 3 years of age
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 – treat with sulfonylureas, not insulin
  - Congenital hyperinsulinism – HI/HA – treat with antiseizure medicines, diazoxide
Treatable Metabolic Epilepsies

- **Vitamin Responsive Disorders**
  - Pyridoxine, P5P, Folinic acid, Biotin

- **Transportopathies**
  - GLUT1, Cerebral Folate Deficiency, Thiamine Transporter

- **Amino and Organic Acid Disorders**
  - MSUD, propionic, isovaleric, cobalamin C

- **Lysosomal Storage Diseases**
  - LINCL/CLN2

- **Mitochondrial Disorders**
  - PDHC deficiency

- **Purine Synthesis Disorders**
  - MoCo deficiency type A

- **Urea Cycle Disorders**
  - OTC deficiency

- **Neurotransmitter Disorders**
  - BH4, GABA-transaminase

- **Disorders of Glucose Homeostasis**
  - DEND, HI/HA
Audience Response #3

- In a neonate with intractable seizures responsive to vitamin B6 with normal pipecolic acid and ALDH7A1 sequencing, which of the following is the most likely diagnosis?
  - A. PNPO deficiency
  - B. Biotinidase deficiency
  - C. Carnitine deficiency
  - D. Folate deficiency
ARS #3 - ANSWER

• In a neonate with intractable seizures responsive to vitamin B6 with normal pipecolic acid and ALDH7A1 sequencing, which is the most likely diagnosis?

* A. PNPO deficiency
B. Biotinidase deficiency
C. Carnitine deficiency
D. Folate deficiency

ARS #4

Which of the following is true regarding late infantile neuronal ceroid lipofuscinosis (NCL, also known as CLN2)?

- A. Presents as myoclonic seizures in a 2-4 year old child
- B. EEG shows photoparoxymsmal response at slow strobe rates (1-3 Hz)
- C. Recombinant enzyme replacement therapy approved only as intraventricular administration
- D. All of the above
ARS #4 - Answer

Which of the following is true regarding CLN2?

- A. Presents as myoclonic seizures in a 2-4 year old child
- B. EEG shows photoparoxysmal response at slow strobe rates (1-3 Hz)
- C. Recombinant enzyme replacement therapy approved only as intraventricular administration
- D. All of the above

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Diagnosing Genetic Epilepsies – Impact on Treatment
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