Neurometabolic Disorders

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Disclosures

• None

Acknowledgement – Neela Sahai, MD
Learning Objectives

• Clues you are dealing with a metabolic disorder
• Hallmarks of the major classes of metabolic disorders
• Diagnostic and treatment strategies
Importance

• Rare, but in aggregate significant burden of pediatric morbidity
• Timely institution of specific treatments may prevent permanent neurological impairment
• Familial implications
Inborn Errors of Metabolism

- Single gene defects
- Defects in an enzyme or transport protein
- Abnormalities in the synthesis or catabolism of proteins, carbohydrates, fats, or complex molecules.
- Individually rare but collectively numerous
Neurological Manifestations

Common in IEM, may be only manifestation

- Developmental delay
- Visual/auditory loss
- Ataxia, Encephalopathies, myelopathies, neuropathies, seizures, brain dysgenesis.....
- Adult onset – psychiatric, aggression, mood/behavioral disorders
- Neuroimaging often helpful
Imaging Findings in IEM

Suspected IEM disease

- Predominant WM disease
  - Hypomyelination disorders
    - PMD
    - PMLD
    - 18q- syndrome
    - HABC syndrome
    - Salla disease
  - Early involvement of subcortical U fibers
    - Canavan disease
    - Kearns-Sayre syndrome
    - Urea cycle defects
  - Global involvement of WM
    - MLC
    - Vanishing WM
    - End stage of all progressive WM disorders
  - Frontal WM predominance
    - Alexander disease
    - Frontal variant of X-ALD
    - Juvenile and adult form of MLD
  - Multifocal WM abnormalities
    - Mitochondrial defects
    - Zellweger syndrome
    - Mucopolysaccharidosis
  - Predominant involvement of deep WM and CST
    - X-ALD
    - Infantile Refsum disease

- Other WM disorders
  - Parietooccipital WM predominance
    - X-ALD
    - Krabbe disease
    - Late infantile MLD

- Predominant gray matter disease
  - Corpus striatum involvement
    - Globus pallidus involvement
    - Glutaric aciduria type 1
    - Propionic academia
    - Leigh disease
    - MELAS syndrome
  - Methylmalonic academia
  - MSUD

- Mixed gray matter and WM disease
  - WM and thalamus involvement
    - Krabbe disease
  - WM and corpus striatum involvement
    - Glutaric aciduria type 1
    - Propionic academia
    - Leigh disease
    - MELAS syndrome
  - WM and globus pallidus involvement
    - Canavan disease
    - Methylmalonic academia
    - MSUD
    - Urea cycle disorders

* - macrocephaly, ** enhancement

Challenges in Diagnosis

• Common non-specific symptoms
  – Poor feeding
  – hypotonia
  – Sepsis
  – Vomiting and dehydration
  – Developmental delay, behavioral problems
  – Seizures

• Clinical Heterogeneity
  – Symptoms, onset, progression
Clues to Diagnosis

- Prior affected/abnormal/lost child
- Parental consanguinity
- Developmental regression or plateau
- Body/urine odor, micro/macrocephaly, Sz
- Dysmorphology, “coarse features”
- Hepatomegaly, skeletal anomalies
- Episodic decompensations
Clinical Presentations

- Acute symptoms in neonatal period
- Intermittent/Recurrent symptoms
- Later-onset acute symptoms
- Chronic and progressive non specific symptoms
- Specific and permanent symptoms
Neonatal Presentation

• Full term normal newborn that deteriorates without apparent clinical cause
  – Seizures
  – Feeding difficulties
  – Hypotonia
  – Lethargy
  – Vomiting/dehydration
  – Respiratory distress
Juvenile Onset

• Episodic decompensations
  – With catabolism, intake specific food (protein)
  – With fever, exercise

• Symptoms
  – Poor feeding, vomiting, lethargy, Sz, MSΔ
  – Metabolic – acidosis, hypoglycemia, hyperammonemia
  – Ataxia
  – Death
Chronic progressive

- Loss of motor, cognitive, speech abilities
- Systemic findings
  - Skeletal, HSM, ophthalmologic (retina, lens)
- Coarse features
- New onset seizures, spasticity, hyperreflexia, ataxis
Clinical Associations

- **Psychosis/catatonia** — Urea cycle disorders, Neimann Pick Type C, acute intermittent porphyria, hereditary coporphyria, homocystinuria, Tay Sachs, Wilsons
- **Peripheral neuropathy** — Fabry disease, porphyria, Vit (B12, E, B1) def, POLG1, mitochondrial DOs
- **Neutropenia** — organic acidurias, GSD Ib
- **Macrocephaly**— Glutaric aciduria Type I (+ICH), D-2-hydroxyglutaric aciduria, Canavan disease, Alexander, Megalencephalic leukodystrophy
- **Progressive external ophthalmoplegia** - ANT1, Twinkle, POLG1, myotonic dystrophy, SCA, MNGIE
Pathophysiology

- Toxic accumulation of metabolites
- Impaired energy production/utilization
- Decreased synthesis or catabolism of complex molecules
Toxic Metabolites

• Amino acid (MSUD, PKU)
• Organic acidurias (MMA, PA, IVA)
• Carbohydrate (galactosemia, fructose intolerance)
• Cholesterol (Smith Lemli Opitz, Niemann Pick Type C)
• Copper (Menkes, Wilsons)
• Neurotransmitters (tetrahydrobiopterin def)
Toxic Metabolites - Features

- Usually not dysmorphic
- Intervals without symptoms
- Acute, episodic, or chronic decompensation
- Triggers – ingestions, illness, fasting

- DX – lab testing
- Rx – prevent catabolism, diet, clearance
Newborn Screening - PKU

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**Laboratory Values**
- **GABA**: 19.00 mg/dL
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**Medical History**
- Newborn screening for PKU.
PKU

- Severe ID
- Postnatal microcephaly
- Behavioral DO, ASDs
- Seizures
- Rashes
- Decreased pigmentation
- Odor — “mousy”, “musty” (phenyl lactate, phenyl pyruvate)

High signal intensity in white matter regions around anterior and posterior horns of both lateral ventricles and brain atrophy in phenylketonuria
Newborn Screening ACT Sheet
[Increased Phenylalanine]
Phenylketonuria (PKU)

Differential Diagnosis: Phenylketonuria (Classical PKU); non-PKU mild hyperphenylalaninemia; porin defects; transient hyperphenylalaninemia.

Condition Description: In PKU the phenylalanine from ingested protein cannot be metabolized to tyrosine because of deficient liver phenylalanine hydroxylase (PAH). This causes elevated phenylalanine. Phenylalanine defects result from deficiency of tetrahydrobiopterin (BH4), the cofactor for PAH and other hydroxylases. This produces not only increased phenylalanine but also neurotransmitter deficiencies.

**YOU SHOULD TAKE THE FOLLOWING ACTIONS IMMEDIATELY:**
- Contact family immediately to inform them of the newborn screening result.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn and refer as appropriate.
- Initiate confirmatory diagnostic tests in consultation with metabolic specialist.
- Provide the family with basic information about PKU and dietary management.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma amino acid analysis which shows increased phenylalanine without increased tyrosine (increased phenylalanine/tyrosine ratio). Urine phenylalanine and red blood cell D-4HPR assay will identify patients defects. Consider PAH mutation testing.

Clinical Considerations: Asymptomatic in the neonate. If untreated PKU will cause irreversible mental retardation, hyperactivity, autistic-like features, and seizures. Treatment will usually prevent these symptoms. Phenylalanine defects cause severe neurologic disease (developmental delay/asthenia) and require specific therapy.

Additional Information:
- Gene Reviews
- Genetics Home Reference
- Clinical Services
  - PKU
  - Tryptophan Hydroxylase Deficiency
- Referral (local, state, regional and national):
  - Testing
  - Clinical Services
  - Find Genetic Services

http://www.ncbi.nlm.nih.gov/books/NBK55827/
Organic Acid Disorders

“CLASSICAL / TYPICAL”
- Metabolic abnormalities
- Systemic involvement (including neurological)

“CEREBRAL”
- Metabolic derangement absent
- Exclusively neurological

- Propionic Acidemia
- Methylmalonic Acidemia (+Cbl A,B,C def)
- Isovaleric Acidemia
- Multiple Carboxylase Deficiency
- Multiple Co-A Dehydrogenase Deficiency (Glutaric Acidemia, Type 2)
- Maple Syrup Urine Disease

- Glutaric Acidemia-I
- Succinic Semialdehyde Dehydrogenase Deficiency
- N-acetylaspartic Deficiency
- L-2 hydroxyglutaric Aciduria
Catabolism of Branched Chain Amino Acids

- **Leucine**
  - 2-oxocaproic acid
  - Isovaleryl-CoA
  - 3 methylcrotonyl-CoA
  - 3-hydroxy 3-methyl-glutaryl-CoA
  - Acetoacetate

- **Isoleucine**
  - 2-oxo-3-methyl-valeric acid
  - 2-methylbutyryl-CoA
  - 2-methyl-acetoacetyl-CoA
  - Acetyl-CoA

- **Valine**
  - 2-oxoisovaleric acid
  - Isobutryl-CoA
  - 3-hydroxy isobutyric acid
  - 3-methylmalonic semialdehyde

**Pathways and Enzyme Deficiencies**

- **MSUD**
  - Isovaleryl-CoA
- **IVA**
  - 3 methylcrotonyl-CoA
- **PA**
  - Methylmalonyl-CoA
- **MMA**
  - Succinyl-CoA
Acute Presentation

- Poor feeding
- Vomiting
- Lethargy/Change in neurological status
- Respiratory distress
- Abnormal muscle tone
- Seizures

Age of Onset & Severity Variable
General Laboratory Findings

- Metabolic acidosis with increased anion gap
- Ketosis
- Hyperammononemia
- Hypoglycemia
- Neutropenia
- Thrombocytopenia
- Elevated amylase/lipase
Diagnostic Testing

- Urine organic acid analysis by GC/MS
- Plasma amino acid analysis
  - Elevated glycine
  - Branched chain amino acids increased in MSUD
  - Otherwise, typically normal
- Plasma acylcarnitine profile
- Urinary acylglycine profile
Non-Acute Presentation

- Developmental delays +/- Seizures
- Failure to thrive
- Chronic vomiting
- Hypotonia
- Recurrent infections
- Recurrent pancreatitis
- Cardiomyopathy (especially PA)
- Renal Disease
- Odors (Sweaty Feet in IVA, MADD; Burnt Sugar in MSUD)
Neurological Complications

- Metabolic “stroke” (acute or progressive extrapyramidal symptoms): MMA, PA, IVA
- Optic atrophy and retinitis: MMA, PA

Evidence suggests optic atrophy and stroke (and cardiomyopathy) due to secondary defects in respiratory chain.
Delayed Brain Maturation

Myelination delay, Immature gyral pattern, Incomplete opercularization, Hypoplastic corpus callosum cerebellar vermis

Basal Ganglia Lesions
- Pallidum
- Putamen
- Caudate

Progressive White Matter Changes
- Irreversible volume loss (predominantly supratentorial atrophy).

Brainstem and Cerebellar Changes
Imaging: Acute Presentation

MRI of MMA patient aged 20 days
Bilateral lesions of the pallidum with swelling and restricted diffusion as the most prominent finding

MRI at age 12 months:
D. Severely delayed myelination
E. The pallidum appears slightly T2 hyperintense, but this is not definitely abnormal at a maturation stage of 6 months
F. Sagittal images demonstrate a thinned corpus callosum dorsally and a wide foramen of Magendi, the latter apparently due to slight volume reduction of the inferior vermis.

Abnormal Signal in Bilateral Basal Ganglia and Brain Atrophy in an MRI from a 4-year-old boy with propionic-acidemia
Treatment

- Presymptomatic treatment
  - Dietary Treatment: Reduce intake of offending amino acids via restriction of natural protein while maintaining a sufficient intake of essential nutrients and energy substrates)
  - Amino acid supplements
  - Carnitine
  - Cofactors
- Early aggressive treatment of intercurrent illness
- Management of metabolic crisis
- Treatment of manifestations
“Cerebral” Organic Acid Disorders

- Metabolic abnormalities generally absent
- Elevation of diagnostic metabolites (organic acids) may be slight.
- Progressive neurological symptoms
  - Epilepsy • Macrocephaly • Metabolic stroke
  - Extrapyramidal symptoms • Ataxia • Myoclonus
- Progressive findings on neuro-imaging
  - Disturbances of myelination
  - Cerebellar atrophy
  - Frontotemporal atrophy
  - Hypodensities/infarcts of basal ganglia
  - Symmetrical pathology apparently independent of vascular supply.
Glutaric Aciduria - Type I

- Macrocephaly at birth (~50%)
- Soft neurological findings: Hypotonia
- Acute encephalopathic crisis at 3–18 months
  - Often but not always precipitated by intercurrent illness
  - Rapid (24-48 hrs) loss of neurons in caudate and putamen
  - Subsequent dystonia, choreoathetosis, significant motor disabilities
  - Cognitive abilities are often preserved till late in course
- Episodes may be recurrent, but disability most often due to a single episode of acute striatal necrosis
- Clinical Spectrum: Developmental delays from birth to asymptomatic case
MRI Findings: GA-I

A, B. Frontotemporal atrophy
C. High signal intensities in caudate and putamen
D. Edema with acute episode
E. Eventual atrophy caudate, putamen
F. Subdural hygromas, hemorrhages

Glutaric Aciduria - Type I

**Diagnosis:**
- UOA- Glutaric & 3-hydroxyglutaric acids
- Plasma acylcarnitines- **Glutaryl carnitine (C5DC)***
- Enzyme and GCDH gene analysis

*Note – low excretors missed on NBS

**Pathogenesis:**
- Striatal toxicity of GA
- Metabolites act as glutamate analogs at the NMDA receptors and Glutamate receptors
- Inhibition of GABA synthesis
- Mitochondrial toxicity
GA- I Treatment

- Presymptomatic treatment to prevent encephalopathic crisis & neurological symptoms
  
  - Dietary Treatment: Reduce Lysine intake via restriction of natural protein while maintaining a sufficient intake of essential nutrients and energy substrates
  
  - Lysine free amino acid supplements
  
  - Carnitine
  
  - Riboflavin: In riboflavin responsive cases

- Early aggressive treatment of intercurrent illness (especially before age 6 years)
GA- I: Treatment of Neurological Complications

- Baclofen & diazepam as first line treatment for dystonia.
- Intrathecal baclofen for severe dystonia/spasticity.
- Trihexyphenidyl as second-line treatment for dystonia.
- Botulinum toxin as additional therapy for severe focal dystonia.
- Avoid Antiepileptics, L-dopa and amantadine for the therapy of movement disorders in GA-I.
- Long-term benefit of dystonic patients from pallidotomy is uncertain
- Avoid Valproate
Canavan Disease

- Macrocephaly, Hypotonia, Developmental Delays: Apparent by 3-months of age.
- Severe motor delays.
- With age hypotonia gives way to spasticity.
- Optic atrophy may be present. No hearing loss
- Seizures, Sleep disturbances
- Variable life expectancy; usually into teens.
- Clinical Spectrum: Mild form exists
Canavan Disease: MRS

markedly increased level of N-acetylaspartic acid (NAA)

Canavan Disease

Diagnosis:
- Urine-Increased N-acetylaspartate
- Enzyme and ASPA gene analysis

Pathogenesis:
- Deficiency of acetate resulting in impaired oligodendrocyte maturation and myelination
- Oxidative stress induced by NAA
- Excitation of NMDA receptors and Glutamate receptors
- Excess NAA impairs osmotic balance
Canavan Disease: Treatment

- Primarily supportive, trials exist

- **Glyceryltriacetate (4.5 g/kg/d)\(^1\):**
  - 2 infants; Ages 8 months & 1 yr; treated for 4.5 & 6 months respectively.
  - No significant side effects/toxicity observed
  - No motor improvement. (earlier treatment??)

- **Lithium Citrate (45 mg/kg/day)\(^2\):**
  - 6 infants; Mean age 9.5 months treated for 6 weeks.
  - No significant side effects/toxicity observed.
  - Modest drop in NAA
  - Alertness improved but no motor improvement (on GMFT). (stabilized?)
  - Imaging: DTI images (n=2) across CC suggested micro-structural improvement. Modest drop in T1 relaxation times on selected brain areas (CC and FWM)

- **Lipoic Acid (antioxidant)**

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Succinic Semialdehyde Dehydrogenase Deficiency

- Psychomotor retardation
- Hypotonia
- Ataxia
- Seizures (~ 50%)
- Hyperkinetic, aggressive and self-injurious behavior
- Hallucinations
- Sleep disturbances
- Basal ganglia signs (choreoathetosis, dystonia & myoclonus) in few
Succinic Semialdehyde Dehydrogenase Deficiency

Diagnostic Laboratory Investigations

Urinary Organic Acids: Elevated 4-hydroxybutyrate*
Enzyme (Leucocytes) and ALDH5A1 gene analysis

*Volatile – may be missed on UOA (CSF)

Pathogenesis
Downregulation of GABA Receptors
MRI Findings Succinic Semialdehyde Dehydrogenase Deficiency.

T2 hyperintensities
- Globus pallidi (43%)
- Cerebellar dentate nucleus (17%)
- Subcortical white matter (7%)
- Brain stem (7%)

Also cerebral or/and cerebellar atrophy, and delayed myelination.

P. L. Pearl et al. Neurology 2003;60:1413-1417
Succinic Semialdehyde Dehydrogenase Deficiency: Treatment

Management of manifestations

- Antiepileptics:
  - Carbamazepine & Lamotrigine
  - Vigabatrin (irreversible inhibitor of GABA-transaminase) - Inconsistent results.
  - Avoid Valproate

- Neurobehavioral: Methylphenidate, thioridazine, risperidal, fluoxetine, and benzodiazepines.

Under Investigation

- Taurine, rapamycin, SGS-742 GABA-B R antagonist
Amino Acid Disorders

**UREA CYCLE DISORDERS**

**NON KETOTIC HYPERGLYCINEMIA**

**SULFITE OXIDASE DEFICIENCY**

**HOMOCYSTINURIA**

**PHENYLKETONURIA**

Only few examples shown here

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Urea Cycle Disorders

- Glutamine
- Alanine
- Glycine
- Aspartate
- Glutamate

Nitrogen Pool

NAGS: N acetylglutamate synthetase

N acetyl glutamate

Ammonia

CPS: Carbamoylphosphate synthetase

Carbamoyl phosphate

Ornithine transcarboxylase

Citrulline

Mitochondria

Citrulline

ASS: Argininosuccinic synthetase

Argininosuccinate

ASL: Argininosuccinic lyase

Arginine

Urea

Fumarate

Arginase

Ornithine
Urea Cycle Disorders

Nitrogen Pool
- Glutamine
- Alanine
- Glycine
- Aspartate
- Glutamate

- Ammonia
- Carbamoylphosphate synthetase
- N-acetylglutamate synthetase
- Ornithine transcarboxylase
- Argininosuccinic synthetase
- Argininosuccinic lyase
- Arginase

Mitochondria
- Citrulline
- Ornithine
- Argininosuccinicate
- Fumarate

Cytosol
- Ornithine
- Arginine
- Urea

Phenylacetylglutamine
- Phenylbutyrate

Orotic Acid
Acute Presentation

- Hyperammonemonic Encephalopathy
- Rare in Arginase Deficiency
- Hyperventilation is an early finding
- In milder forms triggered by stress/illness
- Outcomes depend on severity and duration of hyperammonemia
- Damage resembles hypoxic-ischemic events or stroke. Lacunar infarcts and white matter disruption are common findings
Urea Cycle Defects

- **NAGS**: Similar to CPS
- **CPS**: Considered most severe; No orotic acid.
- **OTC**: X linked. 15% O₄ hyperammononemia
- **ASS (CIT I)**
- **ASL (ASA)**: Trichorrhexis nodosa. Hepatic enlargement and fibrosis.
- **ARG**: Acute presentation uncommon. Progresssive spasticity most common presentation. Also tremor, ataxia, and choreoathetosis
Diagnosis

- Ammonia
- Electrolytes & Blood Gases
- Plasma Amino Acids
- Urinary Orotic Acid
- Molecular Testing
Treatment

Treatment of Acute Hyperammonemia

• IV Nitrogen Scavenger Drugs
• Hemodialysis
• Supplementation with Arginine, Citrulline & Carbamyl glutamate (depending on disorder)

Long Term Management:

• Dietary restriction of protein
• Use of specialized formulas
• Oral nitrogen-scavenging drugs.
• Supplementation with Arginine, Citrulline & Carbamyl glutamate
• Avoidance of Valproic acid, Prolonged fasting or starvation, Intravenous steroids, Large boluses of protein or amino acids.
Non-Ketotic Hyperglycinemia (Glycine Encephalopathy)

**NEONATAL**
- Progressive lethargy
- Hypotonia
- Myoclonic Jerks
- Apnea

**INFANTILE**
- Hypotonia
- Delays
- Seizures

**SEVERE**
- Limited development (DQ < 20).
- Intractable seizures
- Progressive spasticity
- Swallowing dysfunction

**MILD**
- DQ (20-60).
- Seizures
- Limited spasticity
- Hyperactive
- Choreic movements

**Non-Ketotic Hyperglycinemia (Glycine Encephalopathy)**
Non-Ketotic Hyperglycinemia (Glycine Encephalopathy)

- Brain malformations (Thinning/agenesis of the corpus callosum)
- Delayed myelination
- Atrophy
- High-signal lesions in white matter consistent with vacuolating myelin.
- Abnormal glycine peak by proton MRS

Axial diffusion-weighted MR images in 4 day-old neonate presenting with encephalopathy and respiratory failure. (a) and (b) restricted diffusion in posterior limbs of the internal capsules (arrows). (c) Axial T2 weighted image at the same level shows no signal abnormality. (d, e) Axial diffusion weighted MR images of pons show restricted diffusion in the dorsal midbrain and pons

Non-Ketotic Hyperglycinemia (Glycine Encephalopathy)

**Pathogenesis:**
NMDA Receptor Overstimulation

**Glycine Cleavage Complex**

- Glycine
- CO2
- CH2-NH3
- CH2-THF
- Ammonia
- FADH2
- FAD
- Fe-S
- NFU1
- P
- T
- H
- L

**Diagram Elements:**
- Glycine Cleavage Complex
- FAD
- FADH2
- Fe-S
- NFU1
- P
- CH2-NH3
- CH2-THF
- CO2
- NMDA Receptor Overstimulation
Glycine Cleavage Complex

Gene: GLDC

Gene: GCHS

Gene: AMT

Glycine

SLC6A9

Glycine

CO2

Fe-S

NFU1

H

L

NADH + H+

NAD

5,10 methyleneTHF

Ammonia

THF

CH2-NH3

Gene: GLDC

P

H

T

Gene: AMT

Gene: GCHS
Non-Ketotic Hyperglycinemia (Glycine Encephalopathy) Diagnosis

- Elevated Glycine in Plasma, Urine, CSF
- Elevated CSF/Glycine Ratio
- Elevation of CSF only with SLC6A9

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- Molecular Genetic Testing (*GLDC, AMT, GCSH, NFU1, SLC6A9*)
- Activity of Glycine Cleavage System (80 mg liver tissue)
- $^{13}$C-glycine Breath Test
Non-Ketotic Hyperglycinemia: Treatment

- Benzoate (Sodium) 250-750 mg/kg/day
- N-methyl-D-aspartate receptor antagonists (Ketamine, Felbamate & Dextromethorphan)
- Management of manifestations
- Avoid Valproate
Molybdenum cofactor deficiency

Cysteine
Sulfites
Sulfur dioxide

Sulfate oxidase deficiency
Intractable seizures, infantile spasms
Dysmorphic features
Progressive encephalopathy
Lens dislocation
Eczematous rash
Hyperekplexia

Sulfate oxidase
Sulfate + 2e⁻

xanthine oxidase
Uric acid

Xanthine, hypoxanthine

Xanthine oxidase deficiency
Xanthinuria, low uric acid
Arthropathy, myopathy
Nephropathy, renal failure

Genes – MOCS1, MOSC2, GPHN
Molybdenum cofactor deficiency

Management and treatment

• Antiepileptic's
• Diets low in sulfur containing amino acids along with sulfate supplementation have positive biochemical responses but no lasting neurological improvement.

MoCo type A def – RX (cPMP), a precursor to MoCo.
    stopped Sz, neurotoxicity – no reversal

Genetic therapy with a MOCS1 - future Rx?
Impaired energy production/utilization

- Mitochondrial respiratory chain
- Krebs cycle disorders – PDHD, pyruvate carboxylase
- Fatty acid oxidation defects
- Defects in gluconeogenesis or glycogenosis
Mitochondrial Disorders

- MELAS – mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
- MERRF – myoclonic epilepsy and ragged red fibers
- LHON - Leber hereditary optic neuropathy
- KSS – Kearns-Sayre syndrome
- CPEO – chronic progressive external ophthalmoplegia
- POLG1 – related disorders
- MNGIE – mitochondrial neurogastrointestinal encephalomyopathy
- Primary coenzyme Q10 deficiency
Features

● Multiple systems affected
  – Muscle, brain, heart, endocrine
  – CNS encephalopathy, Sz, dementia, stroke-like episodes, ataxia, spasticity, deafness, ptosis, optic atrophy, retinopathy

● Hypoglycemia, met acidosis, hypotonia, FTT

● Inheritance – maternal (mito), AD, AR (nuclear)

● DX- labs, biopsies, genetic testing

● RX – avoid catabolism, vitamins, supplements
**POLG1 – related disorders**

- Nuclear encoded DNA polymerase subunit gene
- Spectrum of phenotypes
- Similar within a family
- Multisystemic – NOT diabetes or cardiomyopathy
  - Psychiatric, Sz, extrapyramidal symptoms, cerebellar
  - Migraines, stroke-like episodes, SNHL,
  - Retinopathy, ptosis, ophthalmoplegia, Cataracts, cortical visual loss
  - Peripheral neuropathy, DM, ovarian/testicular failure, liver failure, GI dysmotility, CM

**RX**
- AVOID Valproic acid → liver failure
- Supportive care
  - Levodopa for extrapyramidal symptoms

- Alpers-Huttenlocher syndrome
- Childhood myocerebrohepatic syndrome
- Myoclonic epilepsy myopathy sensory ataxia
- Ataxia neuropathy spectrum
- AR/AD progressive external ophthalmoplegia
MNGIE
(mitochondrial neurogastrointestinal encephalomyopathy)

• Thymidine phosphorylase deficiency
  – Phosphorylates thymidine, deoxyuridine
  – Pyrimidine salvage – critical for mtDNA
  – mtDNA deletions, mutations, depletion over time

• Symptoms (mean onset 18 yo, as early as 5 mo)
  – Severe GI dysmotility (pseudoobstruction)
  – Cachexia
  – Ptosis/ophthalmoplegia, SNHL
  – Peripheral sensorimotor neuropathy (paresthesias, pain, foot drop)
  – Asymptomatic leukoencephalopathy

• DX
  – Enzyme assay (Columbia), gene sequencing
MNGIE
(mitochondrial neurogastrointestinal encephalomyopathy)

• **DX**
  - Enzyme assay (Columbia), gene sequencing

• **RX**
  - Supportive
    • GI – nutritional support, attention to swallowing difficulties and airway protection, Rx bacterial overgrowth
    • Neuropathy - amitriptyline, nortriptyline, and gabapentin
    • PT, OT
    • Protect liver – TPN, care with meds metabolized by liver
    • Avoid mito toxic meds – valproate, phenytoin, Tc, metformin, trazadone
Decreased synthesis or catabolism of complex molecules

• Lysosomal & peroxisomal disorders
• Congenital disorders of glycosylation
• Defects in cholesterol synthesis
  – Smith Lemli Opitz, C-4 sterol deethylase
• intracellular trafficking
  – Niemann Pick C
Features

• Often dysmorphic

• Multi-systemic, progressive
  – Central and peripheral NS involvement, coarse features, HSM

• No triggers

• DX – labs, genetic testing

• RX – limited, some enzyme replacements, BMT
The Floppy Baby

POSSIBLE CLUES:
- DTRs ↑
- Alertness ↓
- Microcephaly
- Seizures
- Dysmorphisms
- Apnea

Central / UMN

Head imaging
EEG

Dysmorphic

Genetic/syndromic

ECHO
Abd U/S
Ophtho

Non-dysmorphic

Inborn errors of metabolism / Mitochondrial

TORCH
HIE
Sepsis

Small molecules
VLCFA
CDT
NH3
Lactate
Pyruvate
MR spec

Central / UMN

Muscle bx

Peripheral / LMN

EMG
Electrophysiologic studies
Nerve conduction studies

Inconclusive

AHC

Nerve

Demyelinating vs. axonal

Demyelinating

Botulinum toxin

Nerve bx

Targeted genetic testing

Muscle bx

Muscle

CK
Plasma amino acids
Urine organic acids
CHO def transferrin

POSSIBLE CLUES:
- DTRs ↓/nml
- Bulk ↓
- CK ↑
- Weakness
- Fasciculations

Alexandra Garza Flores, MD
# Neonatal Seizures

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Intoxication</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypoxic-ischemia</td>
<td>• MSUD, MMA, PA, IVA, urea cycle</td>
</tr>
<tr>
<td>Meningitis</td>
<td>• Initial symptom free period</td>
</tr>
<tr>
<td>Hemorrhage/stroke</td>
<td>• Sz, Poor feeding, lethargy, respiratory distress</td>
</tr>
<tr>
<td>Trauma</td>
<td>• High AG metabolic acidosis, ketosis, ↑NH3</td>
</tr>
<tr>
<td>Malformation</td>
<td><strong>Primary Energy Metabolic Defects</strong></td>
</tr>
<tr>
<td>Hypoxemia</td>
<td><strong>Pyruvate metabolism, mitochondrial</strong></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>• Sz, hypotonia, poor feed, lactic acidosis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>• Liver disease, cardiomyopathy, cataracts, hearing loss, renal tubular defects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perxisomal defects</th>
<th><strong>Congenital disorders of Glycosylation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sz, hypotonia, dysmorphic features, cholestasis, renal cysts, ocular abnormalities, hearing loss</td>
<td>Sz, FTT, Dev Delay, hepatopathy, protein losing enteropathy, hypoglycemia, hypotonia, immunological, skin, skeletal abnl</td>
</tr>
</tbody>
</table>

*C. Ficicioglu, D. Bearden / Pediatric Neurology 45 (2011) 283e291*
Isolated Neonatal Seizures

• pyridoxine-dependent seizures
• folinic acid-responsive seizures
• nonketotic hyperglycinemia
• sulfite oxidase deficiency,
• molybdenum cofactor deficiency
• glucose transporter type 1 deficiency
• 4-aminobutyrate aminotransferase (g-aminobutyric acid transferase) deficiency
• congenital neuronal ceroid-lipofuscinosis
• dihydropyrimidine dehydrogenase deficiency, creatine deficiency
• syndromes, and defects of serine biogenesis

NOT DETECTED ON NEWBORN SCREEN

C. Ficicioglu, D. Bearden / Pediatric Neurology 45 (2011) 283e291
# Isolated Neonatal Seizures

## Table 1. Warning signs for inborn errors of metabolism as a cause of isolated neonatal seizures

- Seizures beginning prepartum
- Seizures refractory to conventional antiepileptic drugs
- Progressive worsening of clinical and electroencephalographic abnormalities
- Electroencephalogram indicative of burst suppression or dysrhythmia
- Magnetic resonance imaging findings indicative of prominent brain atrophy
- Magnetic resonance imaging findings indicative of hypoxic-ischemic injury, without an obvious hypoxic insult at delivery
# Treatable Causes of Isolated Neonatal Seizures

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxine-dependent seizures</td>
<td>Pyridoxine (15-30 mg/kg/day)*</td>
</tr>
<tr>
<td>Pyridoxal phosphate-dependent seizures</td>
<td>Pyridoxal-5-phosphate (50-100 mg/kg/day)</td>
</tr>
<tr>
<td>Folinic acid-responsive seizures</td>
<td>Folinic acid (3-5 mg/kg/day) ± pyridoxine</td>
</tr>
<tr>
<td>Glucose transporter type 1 deficiency</td>
<td>Ketogenic diet</td>
</tr>
<tr>
<td>Creatine deficiency syndromes</td>
<td>Creatine (0.35-2 g/kg/day)</td>
</tr>
<tr>
<td>Defects of serine biogenesis</td>
<td>Serine (400-600 mg/kg/day) or glycine (200-300 mg/kg/day)</td>
</tr>
</tbody>
</table>

* The dose should be adjusted according to the response.
Neonatal Seizure Work-up

**Initial evaluation**
- CBC/diff, Urinalysis, blood glucose
- Electrolytes, VBG, Ca, P, Mg, LFT, NH3
- Blood CSF cultures, newborn screen, EEG

**For refractory/undiagnosed Seizures**
- Urine organic acids, plasma amino acids
- Plasma acylcarnitine, lactate/pyruvate, VLCFA
- MRI/MRS
- Homocysteine, uric acid
- Urine purine/pyrimidine, thiosulfate
- Urine/serum guanidinoacetate/creatinine
- Urine creatine/creatinine
- Carbohydrate def transferrin, N-/O-glycans
- Genetic testing – infantile epilepsy panel
## CSF STUDIES

### Metabolic

<table>
<thead>
<tr>
<th>CSF</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ (MET01) Amino Acids</td>
<td>☐ (NC04) Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (Includes Biomarkers for Pyridoxine Responsive Seizures)</td>
</tr>
<tr>
<td>☐ (MET07) Lactate</td>
<td>☐ (NC05) Pyridoxal 5'-phosphate [Pyridox(amine Phosphatase Deficiency + CNS Pyridoxal 5'-phosphate Deficiency]</td>
</tr>
<tr>
<td>☐ (MET11) Pyruvate*</td>
<td>☐ (NC06) Succinyladenosine [Adenylosuccinate Lyase Deficiency]</td>
</tr>
<tr>
<td>☐ (NC01) 5-Methyltetrahydrofolate</td>
<td>☐ (NC07) Sialic Acid [Disorders with Hypomyelination of Unknown Etiology/ Sialic Acid Storage Disorders]</td>
</tr>
<tr>
<td>☐ (NC02) Neopterin [Marker for CNS Immune System Stimulation]</td>
<td>☐ (NC08) Alpha-Aminoadipic Semialdehyde [Pyridoxine-Responsive Seizures]</td>
</tr>
<tr>
<td>☐ (NC03) Neopterin/Tetrahydrobiopterin</td>
<td>☐ (NC09) 4-Hydroxybutyric Acid [Succinic Semialdehyde Dehydrogenase Deficiency]</td>
</tr>
<tr>
<td></td>
<td>☐ (NC10) Glucose [Glucose Transporter Deficiency]</td>
</tr>
</tbody>
</table>
FINAL REMARKS

- High Index of Suspicion
- Initial metabolic investigations
  - Chemistries, CK, LFT’s
  - Ammonia
  - Urinalysis, urinary reducing substances & ketones
  - Lactate, Pyruvate
  - Plasma Amino Acids
  - Plasma Acylcarnitine
  - Urinary Organic Acids
  - CSF
- MRI/MRS
Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement

Zornitza Stark, MD¹, Deborah Schofield, PhD¹,²,³, Khurshid Alam, PhD⁴,⁵, William Wilson, PhD⁵,⁶, Nessie Mupfeki, MHIM⁵,⁶, Ivan Macciocca, MHS⁵,⁶, Rupendra Shrestha, PhD⁷, Susan M. White, MD⁴,⁵ and Clara Gaff, PhD⁴,⁵
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