Pediatric Neurometabolic Disorders

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Neurometabolic Disorders

Objectives

- Overview & Approach
- Testing
- Treatment

- Key Examples
Neurometabolic Disorders

• Inborn Errors of Metabolism (IEMs)
  ◦ Affect synthesis, metabolism, transport or storage of biochemical compounds
  ◦ Many feature significant neurologic dysfunction
Neurometabolic Disorders

- Individually rare
  - Few cases seen over a career
- Collectively significant burden of pediatric morbidity

- Accurate diagnosis important
  - Familial (recurrence risk) implications
    - Prenatal diagnosis
    - Asymptomatic pre-clinical diagnosis in affected siblings
  - Specific treatments that may radically alter individual outcomes averting significant neurologic sequelae
    - Success related to earlier timing of identification & intervention
Neurometabolic Disorders

Genetics

- Mendelian
  - typically autosomal recessive, occasionally X-linked
    - Nuclear DNA
    - cytosolic / mitochondrial DNA
- Non-Mendelian
  - Maternal
    - Mitochondrial DNA
Accurate diagnosis is clinically challenging

- Common non-specific symptoms that mimic more common conditions
  - Vomiting & dehydration
  - Feeding difficulties
  - Sepsis
  - Developmental delay
  - Seizures

- Clinical heterogeneity for same disorder
  - Presenting symptoms
  - Age of onset
  - Rate of progression
  - Intra-familial variability
Neurometabolic Disorders

- Some clinical clues
  - Parental consanguinity
  - Prior unexplained loss of a child
  - Prior affected child with or without a recognized diagnosis
  - Dysmorphology
  - Neonatal encephalopathy
  - Neonatal seizures
  - Developmental regression/plateau
Neurometabolic Disorders

• Some clinical clues
  – Episodic abrupt decompensation (vomiting, dehydration, hypotonia) or symptoms (ataxia, lethargy, obtundation)
  – Hepatosplenomegaly or skeletal changes
  – Multiple organ systems affected (mitochondrial)
  – Myoclonic epilepsy (PME)
  – Leukodystrophy
  – Peripheral Neuropathy
  – Ophthalmologic findings (cherry red spot, corneal clouding)
Neurometabolic Disorders
Modes of Presentation

- Neonatal Metabolic Distress
  - Normal pregnancy, labour & delivery
  - Variable post-natal symptom free interval
  - Unexpected abrupt deterioration
    - Lethargy
    - Hypotonia
    - Respiratory distress
    - Vomiting/dehydration
    - Seizures
  - Negative routine investigations
Neurometabolic Disorders
Modes of Presentation

- Later Onset Acute Symptomatology
  - Recurrent episodes interspersed by symptom free intervals
    - Precipitated by protein intake or conditions provoking protein catabolism or fatty acid mobilization
  - Fever, vaccination, decreased food intake, intense activity
    - Obtundation that may proceed to coma
    - Vomiting & lethargy
    - Ataxia
    - Exercise intolerance with cramping & myalgias
  - Metabolic disturbances - metabolic acidosis, lactic acidosis, hyperammonemia & hypoglycemia
Neurometabolic Disorders
Modes of Presentation

- Chronic Progressive Encephalopathy
  - Gradual onset, insidious progression
  - Loss of previously acquired skills
    - Motor
    - Intellectual
  - White matter involvement frequent
  - Long tract findings
    - Spasticity, hyper-reflexia
  - Extra-neural findings
    - Bones, eye, liver, spleen
Neurometabolic Disorders: CLASSIFICATION

Group 1: Disorders of INTOXICATION
Group 2: Disorders of ENERGY METABOLISM
Group 3: Disorders of COMPLEX MOLECULES
Group 4: Disorders of UNIQUE PATHOPHYSIOLOGY
Neurometabolic Disorders: Group 1: Disorders of INTOXICATION

- This includes disorders of intermediary metabolism that lead to acute and/or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block.
  - amino acid catabolism (PKU, MSUD, etc)
  - most organic acidurias (methylmalonic, propionic, isovaleric)
  - urea cycle disorders (OTC)
  - CHO metabolism (galactosemia & hereditary fructose intolerance)
  - copper metabolism (Wilson's & Menkes)
  - cholesterol metabolism (Niemann-Pick C & Smith-Lemil-Opitz)
  - neurotransmitter metabolism (tetrahydrobiopterine deficiency)
Neurometabolic Disorders:
Group 1: Disorders of INTOXICATION

FEATURES of Group 1

- rarely dysmorphic
  (some UOAs, Menkes, Smith-Lemil-Opitz)
- symptom free interval
- intoxication (acute, intermittent or chronic)
- triggered by fever, intercurrent illness, catabolic states
- diagnosis often w/ laboratory tests
  (PAAs, UOAs, acylcarnitine profile, Cu, ceruloplasmin, NTS, etc)
- treatment with diet restriction, toxin removal & trigger avoidance.
Maple Syrup Urine Disease (MSUD)

- AR
- Disorder of branched-chain amino acid metabolism (leucine, isoleucine & valine)
- Classic (neonatal), Intermediate, Intermittent & Thiamine-Responsive forms.
- The three genes associated with MSUD are BCKDHA (E1a subunit gene), BCKDHB (E1b subunit gene), and DBT (E2 subunit gene).

Management:
- Includes dietary leucine restriction, high-calorie BCAA-free formulas, judicial supplementation with isoleucine and valine and frequent clinical and biochemical monitoring.
- Metabolic decompensation is corrected by treating the precipitating stress while delivering sufficient calories, insulin, free amino acids, isoleucine, and valine to achieve sustained net protein synthesis in tissues.
WILSON’S DISEASE

- AR
- disorder of copper metabolism that can present with hepatic, neurologic &/or psychiatric disturbances:
  - Liver: recurrent jaundice, acute self-limited hepatitis, autoimmune-type hepatitis, fulminant hepatic failure or chronic liver disease.
  - Neurologic: movement disorders (tremors, poor coordination, chorea, rigid dystonia, parkinsonism)
  - Psychiatric: depression, psychosis and, occasionally, intellectual deterioration.
  - Ophthalmologic: Kayser-Fleisher rings & sunflower cataracts
  - Systemic: osteoporosis, renal stones, hemolytic anemia, gallstones and, rarely, cardiomyopathy.
WILSON’S DISEASE

- Age of onset ranges from 3-50 years; symptoms vary among and within families.
- Diagnosis with low serum copper & ceruloplasmin concentrations, increased 24 hr urinary copper excretion, the presence of Kayser-Fleisher rings in the cornea and/or increased hepatic copper concentration.
- ATP7B is the only gene known. Molecular genetic testing is clinically available.
- Treatment includes interfering with copper absorption (zinc), copper chelating therapy (penicillamine or trientine) and dietary restriction of copper.
- Liver transplantation reserved for those who fail medical management.
Neurometabolic Disorders:
Group 2: Disorders of ENERGY METABOLISM

- This includes disorders of intermediary metabolism which lead to deficient energy for the liver, heart, skeletal muscles, brain and other high energy tissues.

  - This group of disorders can be divided into cytoplasmic and mitochondrial energy defects.
Neurometabolic Disorders: Group 2: Disorders of ENERGY METABOLISM

- **Cytoplasmic Defects**... generally less severe & treatable
  - glycogen storage diseases (Pompe’s & McArdle’s)

- **Mitochondrial Defects**... generally severe and untreatable
  - congenital lactic acidemias (defects of pyruvate transporter, pyruvate carboxylase, pyruvate dehydrogenase and the Krebs cycle)
  - mitochondrial & respiratory chain defects (Leigh’s, MERRF, MELAS)
  - fatty acid oxidation defects (carnitine transporter deficiency & MCAD)... partially treatable
FEATURES of Group 2

- dysmorphic features possible, but rare
- common symptom profile: MULTISYSTEMIC due to energy failure in high-energy requiring tissues... brain, heart & muscles.
- hypoglycaemia, hyperlactatemia, hepatomegaly, cardiomyopathy, myopathy, hypotonia, failure to thrive, SIDS (circulatory collapse) and degenerative brain involvement
- diagnosis is very difficult!
  - some screening labs & special tests
  - biopsies & molecular genetic testing needed
MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

- Mitochondrial non-mendelian inheritance
- Multisystem disorder with onset typically in childhood between 2-10 years.
- The most common initial symptoms are generalized tonic-clonic seizures, recurrent headaches, anorexia and recurrent vomiting.
- Stroke-like episodes of transient hemiparesis or cortical blindness. These stroke-like episodes may be associated with altered consciousness and may be recurrent.
  - The cumulative residual effects of the stroke-like episodes gradually lead to permanent impairment.
- Exercise intolerance or proximal limb weakness can be the initial manifestation.
- Sensorineural hearing loss is common.
- Growth failure is common.
MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

- The diagnosis of MELAS is based on a combination of clinical findings and molecular genetic testing.
- Mutations in the mitochondrial DNA (mtDNA) gene MT-TL1 encoding tRNAleu are causative.
  - The most common mutation, present in about 80% of individuals with typical clinical findings, is an A-to-G transition at nucleotide 3243 (m.3243A>G)
- Management: No specific treatment for MELAS exists.
  - Mitochondrial vitamin cocktail
  - L-arginine
  - Symptomatic therapies
Neurometabolic Disorders:
Group 3: Disorders of COMPLEX MOLECULES

- This includes disorders of cellular organelle and the synthesis or catabolism of complex molecules.
  - Lysosomal storage disorders
    (Gangliosidosis I & II, Gaucher, Krabbe, Fabry, etc)
  - Mucopolysaccharidoses and Oligosaccharidoses (Hurler, Hunter, Sanfilippo, etc)
  - Peroxisomal disorders
    (Zellweger spectrum, X-ALD, etc)
  - Congenital disorders of glycosylation
Neurometabolic Disorders:
Group 3: Disorders of COMPLEX MOLECULES

FEATURES of Group 3

◦ dysmorphic features (embryo-fetal abNs) common
◦ symptoms are progressive & permanent; 
  unrelated to triggers
◦ MULTISYSTEMIC: hepatosplenomegaly, skeletal deformities, CNS&PNS white matter abNs and CNS malformations
◦ generally untreatable, but enzyme replacement and bone marrow transplant emerging for specific disorders
Tay-Sachs disease

- AR; hexosaminidase A deficiency
- Infantile-Onset (3-6 months) w/ progressive weakness, loss of motor skills, decreased attentiveness, and increased startle response. Progressive neurodegeneration including: seizures, blindness, spasticity, eventual total incapacitation, and death, usually before age four years.
  ◦ CHEERY RED SPOT!
- The juvenile and late-onset variants of hexosaminidase A deficiency have later onsets, slower progression, and more variable neurologic findings, including: progressive dystonia, spinocerebellar degeneration, motor neuron disease, and, in some individuals with adult-onset disease, a bipolar form of psychosis.
**Differential of Cherry Red Spot**

- GM I
- GM 2 - Tay-Sachs, Sandhoff
- Niemann Pick A & C
- Sialidosis
- Galactosialidosis
Tay-Sachs disease

- The diagnosis relies on the demonstration of absent to near-absent HEX A enzymatic activity in the presence of normal or elevated activity of HEX B.
- Molecular genetic testing of HEXA is clinically available and is used to identify the specific disease-causing mutations in an affected individual to allow for genetic counseling of at-risk family members.
- Management: Treatment is supportive.
Neurometabolic Disorders:
Group 4: Disorders of UNIQUE PATHOPHYSIOLOGY

- This includes disorders that I could not fit into the first 3 categories.
  - Purine and Pyrimidine disorders (Lesch-Nyhan syndrome)
  - Creatine deficiency syndromes
  - Vitamin-responsive disorders (multiple-carboxylase deficiency, pyridoxine deficiency & folinic acid deficiency)
  - GLUT-1

- Other Neurodegenerative diseases (leukodystrophys, NCLs, DNA-repair abNs, etc)
Lesch-Nyhan Syndrome

• X-linked
• Onset < 1 year with hypotonia and psychomotor developmental delay, are evident by age three to six months.
• Within the first few years, extrapyramidal involvement (e.g., dystonia, choreoathetosis, opisthotonos) and pyramidal involvement (e.g., spasticity, hyperreflexia, extensor plantar reflexes) become evident.
• Cognitive impairment and behavioral disturbances emerge between age 2-3 years. Persistent self-injurious behavior is a hallmark of the disease.

• Overproduction of uric acid may lead to deposition of uric acid crystals or calculi in the kidneys, ureters, or bladder.
• Gouty arthritis may occur later in the disease.
Lesch-Nyhan Syndrome

- Screening done with a urinary urate-to-creatinine ratio greater than 2.0, indicating uric acid overproduction (hyperuricemia).
- Hyperuricuria/hyperuricemia is not sensitive or specific enough for diagnosis.
- Hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme activity less than 1.5% of normal in cells from any tissue (e.g., blood, cultured fibroblasts, lymphoblasts) is diagnostic.
- Sequence analysis of HPRT1, the only gene known to be associated with Lesch-Nyhan syndrome, is available on a clinical basis.
- Management: Control of overproduction of uric acid with allopurinol reduces the risk of nephrolithiasis & gouty arthritis, but has no effect on behavioral and neurologic symptoms.
  - Only supportive treatment for behavioral & neurological symptoms.
Neurometabolic Disorders

Investigations

Routine/General Investigations
- CBC, electrolytes, glucose, blood gas
- AST/ALT
- BUN/Cr
- Urinalysis: odor, ketones

Intermediary Metabolism
- Ammonia, lactate, pyruvate, plasma amino acids, urine organic acids
- Acyl-carnitine profile
- Urine Guanidinoacetate & Creatine
- CSF glucose, neurotransmitters
Neurometabolic Disorders Investigations

Complex molecule metabolism

- Lysosomal/Storage disorders:
  - Urine mucopolysaccharides
  - Urine oligosaccharides
  - Specific enzyme studies

- Peroxisomal disorders:
  - Very Long Chain fatty acids
  - Phytanic acid

- Carbohydrate glycoprotein deficiency disorders:
  - Transferrin Isoelectric focusing

- Cholesterol disorders:
  - cholesterol
Neurometabolic Disorders

Investigations

• Electrophysiologic
  – EMG/NCS
    • Myopathy-mitochondrial /fatty acid oxidation defects
    • Neuropathy-metachromatic leukodystrophy, Krabbe
  – EEG
    • PME-sialidosis, MELAS, MERRF, GM1, GM2

• Imaging
  – MRI
    • White matter changes
      – Leukodystrophy/peroxisomal disorders
    • Basal ganglia changes
      – PKAN, organic acidemias, Wilson
Neurometabolic Disorders
Investigations

- Specific enzymatic & molecular analysis
- CSF
  - Lactate
    - Mitochondrial disorders
  - Glucose
    - GLUT1
- Biopsy
  - Muscle
    - Mitochondrial, fatty acid oxidation disorders
  - Nerve
    - Neuroaxonal dystrophies, leukodystrophies
  - Skin
    - PME-neuronal ceroid lipofuscinosi
Neurometabolic Disorders
Treatment Options

- Dietary restrictions & Dietary supplementation (PKU, MSUD, Urea Cycle)
- Avoidance of catabolic states (PAAs & UOAs)
- Alternative energy sources (ketogenic diet in GLUT-1)
- Promotion of alternative pathways
  - Sodium benzoate/Phenylbutyrate in urea cycle disorders
- Metabolic inhibitors
  - Allopurinol in Lesch-Nyhan
- Removal of toxic compounds
  - dialysis in hyperammonemias
  - chelating in Wilson’s
Neurometabolic Disorders

Treatment Options

- Replacement of vitamins
  - Pyridoxine
  - Folinic Acid
- Co-factor activation
  - Cobalamin in methylmalonic acidemia
  - Thiamine in MSUD
  - Thiamine, biotin, riboflavin in mitochondrial disorders
- Protein replacement
  - Enzyme replacement: Fabry’s & Gaucher
  - Bone marrow transplant: Hurler’s, MLD, X-ALD