Childhood clinical presentations of inborn errors of metabolism – clinical and laboratory assessment algorithms

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Pathophysiologic classification:
• disorders that give rise to intoxication
• disorders involving complex molecules
• disorders involving energy metabolism

Common Clinical presentations:
• acute symptoms in the neonatal period
• later onset acute and recurrent attacks
  – coma, ataxia, vomiting, acidosis
• chronic and progressive disorders:
  – digestive, neurological, muscular
• specific and permanent organ symptoms
  – cardiomyopathy, hepatomegaly, lens dislocation

Typical ages of presentation
• Neonatal (catabolism is the normal state of life for the first 48 hours)
• Weaning (usually higher protein intake)
• Childhood viral infections (gastroenteritis, febrile illnesses)
• puberty (menstruation, in females with OTC deficiency)

Characteristic intoxication presentation:
• Child is normal at birth
• Over hours/days: gradual onset of lethargy, poor feeding, poor responsiveness
• Coma, hypotonia
• Seizures
• tachypnoea
• No response to appropriate treatment
  – Eg: non-ketotic hyperglycinemia
  – Maple syrup urine disease
  – Urea cycle defects
  – Mitochondrial disorders

Cardiac presentations:
• cardiac failure, cardiomyopathy with hypotonia, muscle weakness, FTT
  – respiratory chain disorders
  – Pompe disease
  – Fatty acid oxidation disorders
• pericardial effusion, tamponade
  – CDG
• cardiomyopathy, arrhythmias, conduction defects (arrest)
  – fatty acid oxidation defects
  – Lysosomal storage disorders
  – Fabry disease
hepatomegaly in infants
• with hypoglycemia
  – eg glycogen storage diseases I and III
• with jaundice, liver failure hepatocellular necrosis
  – HFI, galactosemia, tyrosinemia type 1, hemochromatosis, respiratory chain disorders
• with cholestatic jaundice, FTT and chronic diarrhoea
  – α-1-antitrypsin deficiency, bile acid defects, peroxisomal defects, Niemann-Pick C, LCHAD
• hepatosplenomegaly, “storage” signs, bone changes, cherry-red spot, vacuolated lymphocytes, FTT, chronic diarrhoea
  – GM1 Gangliosidosis,
  – sialidosis,
  – I-cell disease,
  – Niemann-Pick A,
  – MPS VI and VII,
  – galactosialidosis,
  – CDG
*note that in advanced disease, many non-specific symptoms and signs secondary to liver damage confuse the underlying problem, such as:
  – glycosuria, galactosuria, fructosuria
  – hyperammonemia
  – lacticacidemia,
  – hypoglycemia
  – hypertyrosinemia,
  – Hypermethioninemia
  – Glycogen storage can be an artefact

Hypoglycemia
• Is pathological even in neonates
• Aetiology clues with history/duration of fasting
Episodic encephalopathies: more than 50 % patients with IEM present late
•between attacks child is normal
•onset precipitated by minor virus, fever, constipation
•excessive protein intake, prolonged fast, prolonged exercise
•Specimens best collected at time of illness
–Urine organic and amino acids
–Plasma amino acids, ammonium, lactate, acid-base, glucose etc

Causes of childhood encephalopathy
•Sepsis
•Intoxication
–MSUD, urea cycle defects, galactosemia
•Energy deficiency
–Mitochondrial disorders, Fatty acid oxidation defects, Glycogen storage diseases
•Stroke
–Remember these can be metabolic
eg OTC deficiency, Congenital disorders of glycosylation, homocystinuria, respiratory chain, organic acidemias

•if Episodes occur with viral illnesses/change of feeds, consider
–Urea cycle defects (milder) especially ♀
–Mitochondrial
•Clues – history and simple tests
  - lactate / ammonium (may be N)
  - cerebral imaging (basal ganglia)

Static encephalopathies
•Often multi-system diseases with major neurological features
  –Smith Lemli Opitz syndrome
  –Congenital disorders of glycosylation
  –Glucose transporter deficiencies
•Developmental delay
•Glucose transporter defect
  •Poor CSF transport to brain
  •Seizures (often myoclonic)
  •(rare) prenatal onset
•Acquired postnatal microcephaly
•Diagnosis: perform LP and plasma for CSF: glucose ratio
•Treatment with ketogenic diet

Regression
•a period of normal development followed by loss of skills
•May follow a viral illness
•May follow minor head injury

metabolic causes of regression:
•disorders associated with intermediary metabolism
  –deficient energy production
•eg. mitochondrial respiratory chain defects
• Glutaric aciduria type 1
• Disorders of metallic (copper) metabolism
  – Wilson disease
  – Menkes disease
• Leukodystrophies
• Storage disorders

The importance of making a diagnosis:
1. Parental knowledge / acceptance
2. Prognosis
3. Recurrence risk to parents and siblings
4. Option of prenatal diagnosis in subsequent pregnancies
5. There may be a treatment

Initial approach where an IEM is expected
1. General supportive measures (calories, treat sepsis)
2. “Basic” clinical investigations
  – SMELL (maple syrup, sweaty feet, ketones)
  • Laboratory investigations
    – Simple urine: dip stick tests, pH, (DNPH is never the end of the story)
    – Simple blood: pH, ammonium, lactate (capillary sample if possible), glucose-right tube important (fluoride oxalate)
    calcium, homocysteine
3. Specialist lab investigations:
   - Urine, plasma for organic and amino acid analyses
   - Whole blood on filter paper for acylcarnitine profiles
4. Specialist tests (ask for specialist help)
   - Neurotransmitters, loading studies, enzyme assays, mutation detection

Subsequent testing
– Metabolic autopsy if the child dies.
– Store cultured skin fibroblasts/DNA/blood spots

Specific treatments can be instituted once a diagnosis is made
• Some are expensive
  – Eg. Enzyme replacement therapies, substrate deprivation therapies
• Some are “simple”
  – Eg. Frequent feeds, mannose, ketogenic diet, uncooked corn starch
• Transplantation (bone marrow, liver) may be an option for pre / early symptomatic patients
• Dietary restrictions/modifications for small molecule disorders
  - Typically low protein, carbohydrate-rich, fat rich
• Carnitine/glycine supplementation for some organic acidurias
• Cofactors, eg tetrahydrobiopterin, B12, pyridoxine.