Inborn Error of Metabolism

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Inborn errors of metabolism (IEM) are a heterogeneous group of diseases that may or may not be detected by newborn screening. Early recognition of these disorders is important to institute therapy and to prevent neurologic damage.
• IEM may present with an acute crisis—often with encephalopathy the neonatal period—or with a more indolent, chronic course. In addition to the common presenting symptoms of IEM (listed below), a family history of mental retardation, neonatal death in siblings, or parental consanguinity may increase the suspicion of IEM.
• Findings suggestive of an acute IEM crisis (often confused with sepsis)
• poor feeding
• persistent vomiting
• lethargy
• convulsions resistant to IV glucose or calcium
• hypotonia or spasticity
• tachypnea/Kussmaul breathing/apnea
• failure to thrive
• coma
• lack of improvement to any of the above with standard therapy
• Findings suggestive of a chronic IEM course
• developmental delay (especially regression)
• seizures resistant to anticonvulsant therapy
• movement disorder
• peripheral muscle weakness
• cardiomyopathy
• hepatosplenomegaly
• hypoglycemia
• renal failure
• cataracts
• retinal abnormalities
• macrocephaly
• dysmorphic features
• unusual body odors
Workup for suspected IEM

- CBC, differential, and platelets
- serum electrolytes
- arterial blood gas
- serum glucose
workup

- plasma ammonia level
- urine for reducing substances
- urine for organic acids
- urine and blood for amino acids
- urine for ketones if the neonate is hypoglycemic or acidotic
- liver function tests if the child has encephalopathy
Hypoglycemia

- Associated **acidosis** suggests organic acidemias
- Associated **hepatomegaly** or liver failure suggest glycogen storage disorders, galactosemia, or tyrosinemia
- Normal **anion gaps** and **lactic acid levels** suggest hyperinsulinemia or fatty acid oxidation defects
- Associated hyponatremia and hypotension suggest adrenal insufficiency
Emergency treatment

• Remove accumulating metabolites with hemodialysis
• Stop all protein ingestion
• Glucose if patient is hypoglycemic
• Arginine infusion if you suspect a urea cycle defect
• B12 and biotin administration if you suspect an organic acidemia
• Send appropriate labs
• Consultation with geneticist or metabolic specialist
If the patient is dying, it is important to obtain appropriate materials for diagnosis. Urine and separated plasma should be frozen, a tissue sample must be obtained and placed in special medium, and a needle biopsy of the liver should be obtained.
IEM categories with examples

Defects in amino acid metabolism

• Phenylketonuria
• Homocystinuria
• Alcaptonuria
• Hereditary tyrosinemia
Defects in carbohydrate metabolism

- Galactosemia
- Glycogen storage diseases (von Gierke, Pompe)
- Defects in fatty acid oxidation
- Short/medium/long-chain acyl-CoA dehydrogenase deficiency
Urea cycle defects
• Ornithine transcarbamylase deficiency
• Carbamyl phosphate synthetase deficiency

Lysosomal Storage Diseases
• Gangliosidoses (Tay-Sachs, Gaucher, Nieman-Pick)
• Mucopolysacharidoses (Hurler, Hunter)

Defects in heme pigment biosynthesis
• Acute intermittent porphyria
Disorders of metal metabolism

- Wilson’s disease
- Hemochromatosis
- Mitochondrial disorders
- MERRF
Interesting associations between body/urine odor and IEM

- Musty/mousy = phenylketonuria
- Boiled cabbage = tyrosinemia, hypermethioninemia
- Maple syrup = maple syrup urine disease
- Rotting fish = trimethylaminuria
- Sweaty feet = isovaleric academia, glutaric academia (type II)