INBORN ERRORS OF METABOLISM (IEM)
A GENERAL OVERVIEW

Background
1. General Information
   o Classification
     - Traditionally IEM have been classified according to the type of metabolism involved. (note Purine & Pyrimidine disorders, Porphyrias, and Metal metabolism disorders are classified as IEM by only some sources. They are included here in my attempts to be thorough.)
       • Amino Acid Disorders
       • Organic Acidemias (acidurias)
       • Urea Cycle Defects
       • Disorders of Carbohydrate Metabolism
       • Fatty Acid Oxidation Defects
       • Mitochondrial Disorders
       • Peroxisomal Disorders
       • Lysosomal Storage Diseases
       • Purine and Pyrimidine Disorders
       • Porphyrias
       • Metal Metabolism Disorders
   o Screening
     - Tandem Mass Spectrometry has been mandated in multiple states.
     - Information on current national & state-by-state screening can be found through the online resource: [http://genes-r-us.uthscsa.edu/](http://genes-r-us.uthscsa.edu/) (National Newborn Screening and Genetics Resource Center).

Pathophysiology
1. Pathology of Disease:
   o IEM occur when an enzyme or its cofactor(s) are either absent or abnormal and as a result, leads to an accumulation of substrate or deficiency of metabolic products.
   o The physiologic manifestations of an IEM are dependent on the specific metabolite(s) involved.
2. Incidence
   o There is no consensus on the incidence of IEM
   o Most estimates are regionally specific, and exhibit significant variation between different racial and ethnic groups.
   o One estimate of the collective incidence of IEM was around 1:1500 persons
3. Risk Factors
   o Positive Familial History (modes of inheritance of common IEM):
     - Autosomal dominant:
       • Marfan syndrome
       • Acute intermittent porphyria
       • Familial hypercholesterolemia
     - Autosomal recessive:
       • PKU (Phenylketonuria)
• MSUD (Maple syrup urine disease)
• Glycogen storage disease
• Galactosemia
• Organic acidurias
• MCAD (medium chain acylCoA dehydrogenase deficiency)
• Zellewerger syndrome
  ▪ X-linked recessive:
    • Ornithine carbamylase deficiency
    • Fabry disease
    • Pyruvate dehydrogenase deficiency
  ▪ Mitochondrial:
    • Kearns-Sayre syndrome
    • Leigh syndrome

**Diagnostics**

1. Presentation
   o Onset & Severity may vary with:
     ▪ individual disease processes/severity of disease
     ▪ age of individual
     ▪ changes in:
       • diet/fasting
       • hydration/dehydration
       • exercise/exertion/stress
       • concurrent illness/infection/trauma
       • medications/supplements
   o Symptomatic Infants:
     ▪ The clinical picture varies between different metabolic disorders. However, there are general characteristics that are common.
     • Afflicted individuals are usually asymptomatic in the early stages of most inborn metabolic disorders.
     • Early signs of an IEM include (Acute presentation):
       o Lethargy
       o Decreased appetite/feeding
       o Vomiting
       o Tachypnea (associated with acidosis)
       o Decreased perfusion
       o seizures
     • As the metabolic derangement progresses, so does its manifestations
       o Increasing stupor or coma
       o Progressive neuromuscular abnormalities
         ▪ tone (increased or decreased)
         ▪ spasticity
         ▪ posturing (opisthotonus, fisting)
         ▪ movements (lip smacking, tongue thrusting, myoclonic jerks)
   o Symptomatic Older Infants & Children (Chronic presentation)
     ▪ Paroxysmal stupor/lethargy
     ▪ Emesis
- Failure to thrive
- Organomegaly (classically hepatosplenomegally)
- Neurometabolic findings
  - Macro/microcephaly
  - Hypotonia
  - Hypertonia +/- spasticity
  - seizures
  - Skeletal abnormalities
  - Coarse facial features
  - Macular or retinal changes
  - Corneal clouding
  - Skin changes
- Regression of previously achieved developmental milestones.
  - Loss of cognitive milestones
  - Loss of expressive/receptive language abilities
- Progressive decline/deficits in attention, focus, and/or concentration.
- Maladaptive behavioral changes/decline

2. Diagnostic testing:
   - Initial Laboratory Investigations
     - Blood
       - CBC (complete blood count)
       - CMP (complete metabolic panel/chem12)
         - Hepatic & Renal Function
         - Electrolytes
         - Uric Acid
         - Serum Ammonia
           - Obtain without tourniquet
           - Transport on ice for immediate analysis
       - ABG (arterial blood gas)
     - Urine
       - Urinalysis
       - pH
       - color
       - odor
       - specific gravity
       - ketones
       - Urine-reducing substances
   - Additional Laboratory Investigations
     - Blood/Plasma
       - quantitative amino acids
       - lactate
         - Obtain without tourniquet
         - Transport on ice for immediate analysis
       - pyruvate
         - Obtain without tourniquet
         - Transport on ice for immediate analysis
         - Collect in perchlorate to prevent degradation
       - aldolase, creatine kinase
       - acyl carnitine kinase
• lipid Profile
  • Urine
    • qualitative amino acids
    • organic acids
    • myoglobin
  • Imaging
    • MRI brain
    • echocardiogram
  • Biopsy
    • muscle
    • skin
  • Genetic
    • as indicated
  • Laboratory findings & likely metabolism involved
    • Metabolic Acidosis with:
      • Anion gap
        o Organic Acidemias
    • Respiratory Alkalosis
      • Urea Cycle Disorders
    • Hyperammonemia
      • Urea Cycle Disorders
      • Organic Acidemias
    • Lactic acidosis
      • Mitochondrial disorders
      • Glycogen storage diseases
      • Disorders of Glyconeogenesis
      • Disorders of Pyruvate metabolism
      • Organic acidemias
      • Disorders of fatty acid oxidation
      • Aminoacidurias
    • High lactate/pyruvate ratio (normal: 10/1 to 20/1)
      • Mitochondrial disorders
      • Pyruvate carboxylase deficiency
    • Acylcarnitine profile (abnormal)
      • Disorders of fatty acid oxidation
      • Organic acidemias
    • Hypoglycemia
      • with ketosis
        o Glycogen storage diseases
        o Organic acidemias
      • without ketosis
        o Glycogen storage diseases
        o Maple syrup urine disease
        o Disorders of fatty acid oxidation
        o Disorders of ketogenesis
    • Quantitative amino acid profiles
      • Patterns are specific for individual disorders
    • Urine organic acids
      • Patterns are specific for individual disorders
Management

1. Specific to individual disorders and is outside the scope of this general overview.

References


Author: Michel Ritenuti, MD, Penn State Hershey Medical Center, PA

Editor: Dongsheng Jiang, MD, Penn State Hershey Medical Center, PA