INBORN ERRORS OF METABOLISM (IEM)
A GENERAL OVERVIEW

Background

1. General Information
    - Classification
        - Traditionaly 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 Dissorders
            - Organic Acidemias (acidurias)
            - Urea Cycle Defects
            - Dissorders of Carbohydrate Metabolism
            - Fatty Acid Oxidation Defects
            - Mitochondrial Disorders
            - Peroxisomal Dissorders
            - Lysosomal Storage Disseases
            - Purine and Pyrimidine Disorders
            - Porphyrias
            - Metal Metabolism Dissorders
    - 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/ (National Newborn Screening and Genetics Resource Center).

Pathophysiology

1. Pathology of Disease:
    - 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.
    - The physiologic manifestations of an IEM are dependent on the specific metabolite(s) involved.
2. Incidence
    - There is no consensus on the incidence of IEM
    - Most estimates are regionally specific, and exhibit significant variation between different racial and ethnic groups.
    - One estimate of the collective incidence of IEM was around 1:1500 persons
3. Risk Factors
    - 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
   - 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
   - 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):
         - Lethargy
         - Decreased appetite / feeding
         - Vomiting
         - Tachypnea (associated with acidosis)
         - Decreased perfusion
         - seizures
       - As the metabolic derangement progresses, so does its manifestations
         - Increasing stupor or coma
         - Progressive neuromuscular abnormalities
           - tone (increased or decreased)
           - spasticity
           - posturing (opisthotonus, fisting)
           - movements (lip smacking, tongue thrusting, myoclonic jerks)
   - 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 achieves 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 degredation
            - aldolase, creatine kinase
            - acyl carnitine kinase

            - lipid Profile
        - Urine
            - quantitative 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
                - *Organic Acidemias*
        - Respiratory Alkalosis
            - *Urea Cycle Dissorders*
        - Hyperammonemia
            - *Urea Cycle Dissorders*
            - *Organic Acidemias*
        - Lactic acidosis
            - *Mitochondrial disorders*
            - *Glycogen storage diseases*
            - *Dissorders of Glyconeogenesis*
            - *Dissorders of Pyruvate metabolism*
            - *Organic acidemias*
            - *Dissorders of fatty acid oxidation*
            - *Aminoacidurias*
        - High lactate/pyruvate ratio (normal: 10/1 to 20/1)
            - *Mitochondrial dissorders*
            - *Pyruvate carboxylase deficiency*
        - Acylcarnitine profile (abnormal)
            - *Dissorders of fatty acid oxidation*
            - *Organic acidemias*
        - Hypoglycemia
            - with ketosis
                - *Glycogen storage diseases*
                - *Organic acidemias*
            - without ketosis
                - *Glycogen storage diseases*
                - *Maple syrup urine disease*
                - *Dissorders of fatty acid oxidation*
                - *Dissorders of ketogenesis*
        - Quantitative amino acid profiles
            - Pattens are specific for individual dissorders
        - Urine organic acids
            - Pattens are specific for individual dissorders

Management

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

References

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