INBORN ERRORS OF METABOLISM

INTRODUCTION (RAMONA WARREN, M.D. 9/2013)
Inborn errors of metabolism are a diverse set of conditions. This PEM Guide will review two major classes of inborn errors: the organic acidurias and the urea cycle defects as well as one specific entity: congenital adrenal hyperplasia.

CATEGORIES – INBORN ERRORS OF METABOLISM
Carbohydrate metabolism disorders – e.g. Galactosemia
Urea cycle defects*
Fatty acid and mitochondrial metabolism defects
Organic acid disorders*
Amino acid disorders
Lysosomal storage disorders
Peroxisomal disorders
Porphyrias
Purine or pyrimidine metabolism disorders
Disorders of steroid metabolism – eg Congenital Adrenal Hyperplasia*
Mitochondrial function defects

Organic Acidurias - In the organic acidurias, enzyme deficiencies result in the accumulation of metabolic or organic acids. Most are related to the impaired catabolism of the carbohydrate portion of amino acids. These patients generally present with a severe anion gap metabolic acidosis. Organic acid accumulation can also lead to abnormalities in the hepatic, neurologic, and hematologic systems (bone marrow suppression).

Urea Cycle Defects The urea cycle defects are enzyme deficiencies in the urea cycle that result in the reduction of catabolism of the ammonia component of amino acids. These patients typically present with neurologic symptoms due to severe hyperammonemia.

Congenital Adrenal Hyperplasia - Congenital adrenal hyperplasia is a type of adrenal insufficiency most commonly due to a deficiency in the enzyme 21 hydroxylase. This results is a deficiency of both glucocorticoid and mineralocorticoid deficiency and an increase in androgenic steroids as a result of increased shunting to alternate synthesis pathways.. There is great variety in the phenotypic presentation of this disorder. Patients may present with acute salt losing crisis at 3-5 weeks, virilization (cliteromegaly or precocious puberty) and non-classic disease (adult presentation with infertility, oligomenorrhea and hirsutism).

NEWBORN SCREENING

Each state conducts specific newborn screening program tests many of which screen for over 50 disorders. The disorders tested for vary from state to state. Not all of the tests are for inborn errors. For example, HIV and sickle cell disease are included. Results are usually available within the first two weeks of life. There are conditions that are 1. Not included in the screening tests. 2. Undetectable in labs at birth and 3. Not present in the first two weeks of life so normal screening does not rule out an inborn error of metabolism

The list of conditions included in the Connecticut screening program and further information regarding the screening program can be found at: http://www.ct.gov/dph/lib/dph/family_health/newborn_screening/pdf/nbs_family_fact_sheet.pdf

PRESENTATION

Calvo et al (Pediatric Emergency Care, 2000) reported a small series of patients that presented to the emergency department and were ultimately diagnosed with an inborn error of metabolism. The most common findings were neurologic signs (85%), ranging from irritability to coma, and the second most common findings were gastrointestinal complaints (58%). Half of the patients presented with a combination of the two. Older children and even adults can present to the ED with a previously undiagnosed Inborn error. This is particularly true of the urea cycle defects, which can present as late as adulthood and congenital adrenal hyperplasia which has a range of phenotypic expression.

The presentation of an inborn error is nonspecific and overlaps considerably with other childhood disease so a high index of suspicion is warranted. The family history can contribute to the diagnosis. A family of unexplained infant deaths or consanguinity should be sought.

INFANT PRESENTATIONS
Acute neurological decline - lethargy or seizures
Gastrointestinal symptoms -poor feeding, vomiting, diarrhea and dehydration – particularly if rehydration doesn't rapidly restore mental status
Tachypnea
Hypoglycemia, or hyperglycemia
Acidosis – with an elevated anion gap
Hyperammonemia in the absence of liver disease

CHILDHOOD PRESENTATIONS
Atypically severe symptoms or rapid deteriorization with mild childhood illnesses
Recurrent episodes of lethargy, emesis leading to alteration of mental status.
Failure to thrive, food aversions
Unexplained seizures, dystonia, myoclonus, hypotonia, ataxia
Mental retardation or cerebral palsy without a clear etiology

Hepatosplenomegaly
Unusual odors (maple syrup, musty, pine)
Disorders of multiple organ systems

DIAGNOSIS

In general, the diagnostic workup of an inborn error is extensive, but a few key laboratory features include: an anion gap metabolic acidosis, hyperammonemia and hypoglycemia or hyperglycemia. If suspicions are high, set aside, on ice, an extra vial of blood, urine, and CSF so there is a sample of each at the baseline state.

PHYSICAL EXAMINATION	
Pulmonary	Effortless (quiet) tachypnea
Cardiac	Cardiomegaly, dysrhythmias
Hepatic	Hepatomegaly
Splenic	Splenomegaly
Neurologic	Altered mental status, hypotonia
Hematologic	Neutropenia, thrombocytopenia
GU	Ambiguous genitalia
General	Unusual rashes, odors, cataracts

ORGANIC ACIDURIAS – LABORATORY DIAGNOSIS	
Accumulation of organic acids	Anion gap metabolic acidosis
Hepatic	Hypoglycemia, hyperammonemia*
Neurologic	Seizures, hypotonia, altered mental status
Hematologic	Neutropenia, thrombocytopenia
Unusual odors	Eg. Maple syrup urine disease
Definitive diagnosis	Urine for organic acids, plasma amino acids
* Not elevated to the extent seen with urea cycle defects	

UREA CYCLE DEFECTS – LABORATORY DIAGNOSIS	
Hyperammonemia	Severely elevated
Electrolytes/ABG	Typically normal, respiratory alkalosis – direct stimulation
Urinalysis	Orotic acids crystals - ornithine transcarbamylase deficiency
Hepatic	Elevate liver enzymes (with severe hyperammonemia)
Definitive diagnosis	Serum amino acid profile, specific enzyme assays
Differential diagnosis	Liver function tests TORCH Infections (Toxoplasmosis, Rubella, Cytomegalovirus and Herpes Virus).

CONGENITAL ADRENAL HYPERPLASIA – DIAGNOSIS	
Adrenal Insufficiency	Shock
Electrolytes	Glucocorticoid deficiency – Hypoglycemia, Metabolic Acidosis Mineralocorticoid deficiency – Hyponatremia, Hyperkalemia
Skin	Hyperpigmentation (due increased ACTH)
Genitalia	Ambiguous genitalia – eg cliteromegaly in females due to the

	increased production of androgens by alternative pathways
Definitive diagnosis	Inadequate production of cortisol and/or aldosterone, Accumulation of precursor hormones. 21-hydroxylase deficiency - 17-hydroxyprogesterone and urinary pregnanetriol

EMS and HOSPITAL MANAGEMENT

After addressing airway, breathing and circulation the primary goals are to removing toxic metabolites and decrease production of toxic intermediaries by preventing catabolism (and promoting anabolism). The severity of the metabolic defects will guide therapy.

ORGANIC ACIDURIAS - MANAGEMENT
Fluid resuscitation
Correct acidosis – $NaHC0_3$ - promotes organic acid excretion
Dextrose – corrects hypoglycemia, promotes anabolism
Avoid precursors – no protein intake (most due to amino acid catabolism)
Deficiency specific therapy – Biotin, Thiamine, Glycine
Consider sepsis evaluation, empiric antibiotics – marrow suppression

UREA CYCLE DEFECTS - MANAGEMENT	
Decrease ammonia production	
	Substrate restriction - proteins
	Dextrose - corrects hypoglycemia, promotes anabolism
	GI tract sterilization – PO Neomycin – prevent bacterial ammonia production
Increase ammonia excretion	
	Fluid resuscitation
	Avoid alkalization – increase NH3 that crosses the blood, brain barrier
	Dialysis or exchange transfusion
	Antidotes – Na benzoate, Na phenylacetate (nitrogen scavengers)
	Liver transplant

CONGENITAL ADRENAL HYPERPLASIA – MANAGEMENT	
Shock (Acidosis)	Fluid resuscitation – Normal Saline - 20 cc/kg bolus Hydrocortisone – 2mg/kg (max 100 mg)
Hypoglycemia	Dextrose, Hydrocortisone
Hyponatremia	Hydrocortisone has some mineralocorticoid activity
Hyperkalemia	No treatment unless arrhythmia then Calcium

In the event of death, important clues to the diagnosis can be obtained from a skin biopsy, and a liver biopsy at the autopsy. The parents and their surviving children will benefit from knowing whether any other children might have or be a carrier for an inheritable condition.