An approach to Inborn errors of metabolism
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Introduction

Also known as biochemical diseases, inherited metabolic disorders are mostly single gene disorders that affect one of the biochemical processes of the body. Most are rare but some are common, for example phenylketonuria (PKU) occurs 1 in 12,000 births (1). Every year in British Columbia, two to three children are born with PKU (2). By detecting PKU or other biochemical diseases early, neonatal disease, mental retardation, and mental illness can be prevented.

Until recently the following diseases were detected by the newborn screening program in BC: congenital hypothyroidism, PKU, galactosemia, and medium chain acyl-CoA dehydrogenase deficiency (3). However, now with the availability of tandem mass spectrometry, it has become possible to screen for up to 30 additional treatable metabolic diseases (4).

Current diseases screened for can be seen at:
http://www.bcwomens.ca/Services/PregnancyBirthNewborns/NewbornCare/NewbornScreeningProgram/default.htm

Basic Anatomy and Physiology

Mostly inherited as autosomal recessive traits, biochemical diseases are due to an enzyme or transport protein defect. This leads to a deficiency and/or a build-up of metabolites. Either the deficiency of essential products or the inability to eliminate precursors is directly responsible for disease manifestations.

Classes of metabolic diseases:

Metabolic diseases can be categorized according to the different nutritional components in which the abbarrent metabolism may be found:

Proteins

- Amino acid metabolism (examples are phenylketonuria and maple syrup urine disease). There is aberrant synthesis or breakdown of amino acids. (Screened for with panels of urine organic acids and serum amino acids.)
- Urea cycle disorders. There is an enzyme deficiency resulting in aberrant degradation of nitrogen compounds. (Screened for with serum ammonia level.)

Carbohydrates

- Disorders of Carbohydrate metabolism
    - Glycogen storage diseases
- Storage diseases
    - Lysosomal storage diseases
    - Peroxisomal disorders

Fats

- Disorders of Fatty Acid metabolism - Mitochondrial disorders (example is Medium Chain Acyl Dehydrogenase deficiency)

Trace elements

- Metal metabolism disorders (Hemochromatosis, Wilson's disease)

Presentation

Fetal development for neonates with inborn errors of metabolism may have been normal, provided that the metabolites are able to cross the placenta and may be metabolized by the mother for the fetus. Often therefore the neonate may be asymptomatic, and may only become symptomatic after the initiation of feeds or with intercurrent illness / long periods of fasting.

Although the clinical picture may vary, infants with metabolic disorders typically present with lethargy, decreased feeding, vomiting, tachypnea (from acidosis), decreased perfusion, and seizures (6).

Toddlers and preschool-aged children present with stagnation or loss of cognitive milestones; loss of expressive language skills; progressive deficits in attention, focus, and concentration; and other behavioral changes. Other non-specific indicators may be developmental regression, growth retardation and seizures. Multiple stillbirths or early childhood deaths on family history may also be suggestive.

Specific disorders are suggested by signs as listed below:

symptom/signs	biochemical disease
vomiting and acidosis after starting on breast milk or formula	amino acid or carbohydrate metabolism
unusual odor of urine or sweat (e.g. burnt sugar smell)	e.g. maple syrup urine disease
hepatosplenomegaly	accumulation of metabolites within the cells of liver and spleen
mental retardation	due to 1) brain atrophy due to harmful circulating metabolites such as PKU or 2) enlarged brain due to inability to metabolize intracellular substances
severe acidosis with high anion gap	abnormal metabolites of amino acid and organic acid metabolism
hyperammonemia	urea cycle and organic acid disorders

Investigations

Initial workup when an inborn error of metabolism is suspected usually includes electrolytes, glucose, lactate, serum ammonia, serum amino acids and urine organic

acids. Based on these results and after consulting metabolic diseases specialists, further investigations may be sought. These may include CSF analyzed for the metabolite in question.

Approach to treatment

Treatment is obviously dependent on the disorder suspected. General principles however are:

1) Removal of toxic compounds – hemodialysis, hemovenovenous filtration, chelators, and compounds that serve as ammonia trapping agents
2) Enhancement of the activity of the deficient enzyme
3) Decreasing the flux through the deficient pathway by restricting precursors in the diet. If an inborn error of metabolism is suspected in a neonate they should be kept NPO but given IV fluids containing dextrose so as to keep the infant anabolic.

Examples of Inborn Errors of Metabolism by Disorder (7)

Disorder	*~Incidence*	*Inheritance*	*Metabolic error*	*Key manifestation*	*Key laboratory test*	*Therapy approach*
Amino acid metabolism						
Phenylketonuria	1:15,000	Autosomal recessive	Phenylalanine hydroxylase (> 98 percent) Biopterin metabolic defects (< 2 percent)	Mental retardation, acquired microcephaly	Plasma phenylalanine concentration	Diet low in phenylalanine hydroxylase
Maple syrup urine disease	1:150,000 (1:1,000 in Mennonites)	Autosomal recessive	Branched-chain a-keto acid dehydro-genase	Acute encephal-opathy, metabolic acidosis, mental retardation	Plasma amino acids and urine organic acids Dinitrophenyl-hydrazine for ketones	Restriction of dietary branched-chain amino acids
Carbohydrate metabolism						
Galactosemia	1:40,000	Autosomal recessive	Galactose 1-phosphate uridyltransferase (most common); galactokinase; epimerase	Hepatocellular dysfunction, cataracts	Enzyme assays, galactose and galactose 1-phosphate assay, molecular assay	Lactose-free diet
Glycogen storage disease, type Ia (von Gierke's disease)	1:100,000	Autosomal recessive	Glucose-6-phosphatase	Hypoglycemia, lactic acidosis, ketosis	Liver biopsy enzyme assay	Corn starch and continuous overnight feeds

Fatty acid oxidation						
Medium-chain acyl-CoA dehydrogenase deficiency	1:15,000	Autosomal recessive	Medium-chain acyl-CoA dehydrogenase	Nonketotic hypoglycemia, acute encephal-opathy, coma, sudden infant death	Urine organic acids, acylcarnitines, gene test	Avoid hypoglycemia, avoid fasting
Lactic acidemia						
Pyruvate dehydrogenase deficiency	1:200,000	X-linked	E_1 subunit defect most common	Hypotonia, psychomotor retardation, failure to thrive, seizures, lactic acidosis	Plasma lactate Skin fibroblast culture for enzyme assay	Correct acidosis; high-fat, low-carbohydrate diet
Lysosomal storage						
Gaucher's disease	1:60,000; type 1-1:900 in Ashkenazi Jews	Autosomal recessive	b-glucocere-brosidase	Coarse facial features, hepatosplen o-megaly	Leukocyte b-glucocere-brosidase assay	Enzyme therapy, bone marrow transplant
Fabry's disease	1:80,000 to 1:117,000	X-linked	a-galactosidase A	Acropares-thesias, angio-keratomas hypohidrosis, corneal opacities, renal insufficiency	Leukocyte a-galactosidase A assay	Enzyme replacement therapy
Hurler's syndrome	1:100,000	Autosomal recessive	a-l-iduronidase	Coarse facial features, hepatosplen o-megaly	Urine mucopoly-saccharides Leukocyte a-l-iduronidase assay	Bone marrow transplant
Organic aciduria						
Methylmalonicaciduria	1:20,000	Autosomal recessive	Methylmalonyl-CoA mutase, cobalamin metabolism	Acute encephalo-pathy, metabolic acidosis, hypera-mmonemia	Urine organic acids Skin fibroblasts for enzyme assay	Sodium bicarbonate, carnitine, vitamin B_{12}, low-protein diet, liver transplant
Propionic aciduria	1:50,000	Autosomal recessive	Propionyl-CoA carboxylase	Metabolic acidosis, hypera-mmonemia	Urine organic acids	Dialysis, bicarbonate, sodium benzoate, carnitine, low-protein diet, liver transplant
Peroxisomes						
Zellweger syndrome	1:50,000	Autosomal recessive	Peroxisome membrane protein	Hypotonia, seizures, liver dysfunction	Plasma very-long-chain fatty acids	No specific treatment available

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