

Inborn error of metabolism

Inborn errors of metabolism comprise a large class of **genetic diseases** involving disorders of **metabolism**. The majority are due to defects of single **genes** that code for **enzymes** that facilitate conversion of various substances (**substrates**) into others (**products**). In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds. Inborn errors of metabolism are now often referred to as **congenital metabolic diseases** or **inherited metabolic diseases**, and these terms are considered synonymous.

The term ***inborn error of metabolism*** was coined by a British physician, **Archibald Garrod** (1857–1936), in the early 20th century (1908). He is known for work that prefigured the "**one gene, one enzyme**" **hypothesis**, based on his studies on the nature and inheritance of **alkaptonuria**. His seminal text, ***Inborn Errors of Metabolism*** was published in 1923.

Major categories of inherited metabolic diseases

Traditionally the inherited metabolic diseases were categorized as disorders of **carbohydrate** metabolism, **amino acid** metabolism, **organic acid** metabolism, or **lysosomal storage diseases**. In recent decades, hundreds of new inherited disorders of metabolism have been discovered and the categories have proliferated. Following are some of the major classes of congenital metabolic diseases, with prominent examples of each class.

- **Disorders of amino acid metabolism**
 - E.g., phenylketonuria, maple syrup urine disease, glutaric acidemia type 1
- **Disorders of carbohydrate metabolism**
 - E.g., glycogen storage disease
- **Disorders of organic acid metabolism (organic acidurias)**
 - E.g., alcaptonuria
- **Disorders of fatty acid oxidation and mitochondrial metabolism**
 - E.g., medium chain acyl dehydrogenase deficiency (glutaric acidemia type 2)
- **Disorders of porphyrin metabolism**
 - E.g., acute intermittent porphyria
- **Disorders of purine or pyrimidine metabolism**
 - E.g., Lesch-Nyhan syndrome
- **Disorders of steroid metabolism**

- E.g., congenital adrenal hyperplasia
- **Disorders of mitochondrial function**
 - E.g., Kearns-Sayre syndrome
- **Disorders of peroxisomal function**
 - E.g., Zellweger syndrome
- **Lysosomal storage disorders**
 - E.g., Gaucher's disease
 - E.g., Niemann Pick disease

Incidence

According to a study in British Columbia, the overall incidence of the inborn errors of metabolism included in the survey is at least approximately 40 cases per 100 000 live births (1 in 2500). Other inborn errors of metabolism are estimated to have an incidence of at least another 30 cases per 100 000 live births, totalling 1 in 1,400 births. The included inborn errors of metabolism represented over 10% of single gene disorders in the population.^[1]

Approximately 24 children per 100 000 births (1 in 4,200) have a disease involving amino acids (e.g. PKU), organic acids, primary lactic acidosis, galactosemia, or a urea cycle disease.^[1] Approximately 2.3 children per 100 000 births (1 in 43,000) have some form of glycogen storage disease.^[1] Approximately 8 per 100 000 births (1 in 12,500) have a lysosomal storage disease;^[1] ~3 per 100 000 births (1 in 33,000) have a respiratory chain-based mitochondrial disease and ~3 to 4 per 100 000 of births (~1 in 30,000) have a peroxisomal disorder.^[1]

Manifestations and presentations

Because of the enormous number of these diseases and wide range of systems affected, nearly every "presenting complaint" to a doctor may have a congenital metabolic disease as a possible cause, especially in childhood. The following are examples of potential manifestations affecting each of the major organ systems:

- Growth failure, failure to thrive, weight loss
- Ambiguous genitalia, delayed puberty, precocious puberty
- Developmental delay, seizures, dementia, encephalopathy, stroke
- Deafness, blindness, pain agnosia

- Skin rash, abnormal pigmentation, lack of pigmentation, excessive hair growth, lumps and bumps
- Dental abnormalities
- Immunodeficiency, thrombocytopenia, anemia, enlarged spleen, enlarged lymph nodes
- Many forms of cancer
- Recurrent vomiting, diarrhea, abdominal pain
- Excessive urination, renal failure, dehydration, edema
- Hypotension, heart failure, enlarged heart, hypertension, myocardial infarction
- Hepatomegaly, jaundice, liver failure
- Unusual facial features, congenital malformations
- Excessive breathing (hyperventilation), respiratory failure
- Abnormal behavior, depression, psychosis
- Joint pain, muscle weakness, cramps
- Hypothyroidism, adrenal insufficiency, hypogonadism, diabetes mellitus

Diagnostic techniques

Dozens of congenital metabolic diseases are now detectable by newborn screening tests, especially the expanded testing using mass spectrometry. This is an increasingly common way for the diagnosis to be made and sometimes results in earlier treatment and a better outcome. There is a revolutionary GC/MS based technology with an integrated analytics system, which has now made it possible to test a newborn for over 100 genetic metabolic disorders.

Because of the multiplicity of conditions, many different diagnostic tests are used for screening. An abnormal result is often followed by a subsequent "definitive test" to confirm the suspected diagnosis.

Common screening tests used in the last sixty years:

- Ferric chloride test (turned colors in reaction to various abnormal metabolites in urine)
- Ninhydrin paper chromatography (detected abnormal amino acid patterns)
- Guthrie bacterial inhibition assay (detected a few amino acids in excessive amounts in blood) The dried blood spot can be used for multianalyte testing using Tandem Mass Spectroscopy (MS/MS). This given an indication for a disorder. The same has to be further confirmed by enzyme assays, GC/MS or DNA Testing.
- Quantitative plasma amino acids, quantitative urine amino acids
- Urine organic acids by mass spectrometry

Specific diagnostic tests (or focused screening for a small set of disorders):

- Tissue biopsy or necropsy: liver, muscle, brain, bone marrow
- Skin biopsy and fibroblast cultivation for specific enzyme testing
- Specific DNA testing

Treatment

In the middle of the 20th century the principal treatment for some of the amino acid disorders was restriction of dietary protein and all other care was simply management of complications. In the last two decades, enzyme replacement, gene transfer, and organ transplantation have become available and beneficial for many previously untreatable disorders. Some of the more common or promising therapies are listed:

- **Dietary restriction**
 - E.g., reduction of dietary protein remains a mainstay of treatment for phenylketonuria and other amino acid disorders.
 - **Dietary supplementation or replacement**
 - E.g., cornstarch several times a day helps prevent people with glycogen storage disease from becoming hypoglycemic as quickly.
 - **Vitamins**
 - E.g., thiamine supplementation benefits several types of lactic acidosis.
 - **Intermediary metabolites, compounds, or drugs that facilitate or retard specific metabolic pathways**
 - **Dialysis**
 - **Enzyme replacement** E.g. Acid-alpha glucosidase for Pompe's disease
 - **Gene transfer**
 - **Bone marrow or organ transplantation**
 - **Treatment of symptoms and complications**
 - **Prenatal diagnosis and avoidance of pregnancy or abortion of an affected fetus**
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