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Disorders of Galactose Metabolism

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Introduction

- Three inborn errors of galactose metabolism are known.
- The most important is classic galactosemia due to galactose-1-phosphate uridylyltransferase (GALT) deficiency. A complete or near-complete deficiency is life threatening with multiorgan involvement and longterm complications. Partial deficiency is usually, but not always, benign.

- **Uridine diphosphate galactose 4-epimerase (GALE) deficiency exists in at least two forms. The very rare profound deficiency clinically resembles classical galactosemia. The more frequent partial deficiency is usually benign.**
- **Galactokinase (GALK) deficiency is extremely rare and the most insidious, since it results in the formation of nuclear cataracts without provoking symptoms of intolerance.**

- **The Fanconi-Bickel syndrome is a congenital disorder of galactose transport due to GLUT2 deficiency leading to hypergalactosemia. Other secondary causes of impaired liver handling of galactose in the neonatal period are congenital portosystemic shunting and multiple hepatic arteriovenous malformations.**

Deficiency of Galactose-1-Phosphate Uridyltransferase

- **As over 167 mutations in the GALT gene have been identified, different forms of the deficiency exist.**
- **Infants with complete or near-complete deficiency of the enzyme (classical galactosemia).**
- **Partial transferase deficiency associated with 25% residual GALT activity is usually asymptomatic. It is more frequent than classical galactosemia.**
- **In partial deficiency with only 10% residual GALT activity, there may be liver disease and mental retardation in patients left untreated during early infancy.**

Genetics

- The mode of inheritance is autosomal recessive.
- The birth incidence of classical galactosemia is one in 40,000–60,000. In Ireland it is one in 10,000–20,000.
- The gene is situated on chromosome 9, and over 167 mutations or polymorphisms have been described. Some genotype-phenotype matching is available. For instance, homozygosity for the Q188R mutation, unfortunately prevalent, has been associated with unfavorable clinical outcome.

- Because transferase polymorphism be abundant, partial transferase deficiency is more frequent than classical galactosemia.
- Many allelic variants associated with a partial enzyme defect have been reported, but the best known is the Duarte variant due to a N314D GALT gene mutation that exists in cis with a small deletion in the 5' flanking region.
- Variants such as the Q188R/N314D compound heterozygote can be distinguished by enzyme electrophoresis or DNA analysis. The N314D Duarte variant when combined with the severe Q188R mutation is almost always benign.

Metabolic Disorders

- Individuals with a profound deficiency of GALT can phosphorylate ingested galactose but fail to metabolize galactose-1-phosphate. As a consequence, galactose-1-phosphate and galactose accumulate, and the alternate pathway metabolites, galactitol and galactonate, are formed.
- Cataract formation can be explained by galactitol accumulation. The pathogenesis of the hepatic, renal and cerebral disturbances is less clear but is probably related to the accumulation of galactose-1-phosphate and (perhaps) of galactitol.

Uridine Diphosphate-Galactose 4'-Epimerase Deficiency

- **This disorder exists in at least two forms, both of which are discovered through newborn screening using suitable tests sensitive to both galactose and galactose-1-phosphate in dried blood.**
- **Infants with the mild form appear healthy. The enzyme defect is incomplete; reduced stability and greater than normal requirement for the coenzyme nicotinamide adenine dinucleotide have been described.**

Genetics

- Epimerase deficiency is inherited as an autosomal-recessive trait. The epimerase gene resides on chromosome 1.
- Several mutations have been identified [53–57] and characterized
- including the V94M mutation that was present in a homozygous form in all of the patients tested with a severe phenotype. This enzyme catalyzes the conversion of UDP-N-acetylglucosamine to UDP-N-acetylgalactosamine.

- A compound heterozygous patient (L183P/N34S) of mixed Pakistani/Caucasian origin with a mild form and mental retardation, that may or may not be related to the underlying GALE deficiency.
- As in GALT deficiency, abnormal glycosylation of proteins, that appears to be dependent, at least in part, on lactose consumption, has been reported in severe GALE deficiency and is thought to be a secondary biochemical complication, not primarily related to the genetic defect.

Metabolic disorders

- **The enzyme deficiency provokes an accumulation of UDP galactose after milk feeding. This build-up also results in the accumulation of galactose-1-phosphate**

Galactokinase Deficiency

Genetics

- The mode of inheritance is autosomal recessive.
- In most parts of Europe, in the USA and in Japan, birth incidence is in the order of one in 150,000 to one million. It is higher in the Balkan countries, the former Yugoslavia, Rumania and Bulgaria. In Gypsies, birth incidence was calculated as one in 2,500.

- **Two genes have been reported to encode galactokinase: GK1 on chromosome 17q24 and GK2 on chromosome 15. Many GK1 mutations have now been described. The GK1 P28T mutation was identified as the founder mutation responsible for galactokinase deficiency in Gypsies and in immigrants from Bosnia in Berlin.**

Metabolic defects

- **Persons with GALK deficiency lack the ability to phosphorylate galactose. Consequently, nearly all of the ingested galactose is excreted, either as such or as its reduced metabolite, galactitol, formed by aldose reductase.**
- **As in GALT deficiency, cataracts result from the accumulation of galactitol in the lens, causing osmotic swelling of lens fibers and denaturation of proteins.**

Fanconi-Bickel Syndrome

- **This is a recessively inherited disorder of glucose and galactose transport due to GLUT2 deficiency and is extremely rare.**
- **A few cases have been discovered during newborn screening for galactose in blood.**

Portosystemic Venous Shunting and Hepatic Arterio-Venous Malformations

Portosystemic bypass of splanchnic blood via ductus venosus Arantii or intrahepatic shunts causes alimentary hypergalactosemia, which is discovered during metabolic newborn screening.