GALACTOSEMIA

Lactose, or milk sugar, is broken down into its constituent simple sugars, glucose and galactose, before absorption in the intestine. Galactosemia, which is an increased concentration of galactose in the blood, has many causes. The genetic disorders that cause galactosemia vary in severity from a benign condition to a life-threatening disorder of early infancy. Early diagnosis and treatment of the latter condition can be life saving; hence, newborn screening for this disease has been instituted in many states.

Incidence

Three distinct enzyme deficiencies may lead to galactosemia. The most common of these, galactose 1-phosphate uridyltransferase (GALT) deficiency (OMIM database No. 606999),[81] occurs in approximately 1 in 47000 newborn infants.[82] This disorder is often referred to as "classic galactosemia." Galactokinase (GALK) deficiency (OMIM database No. 230200)[81] seems to be very rare, although there have been no large population studies to assess its incidence. One study found that 1% of North American people were carriers, suggesting a disease frequency of 1 in 40000.[83] However, a newborn screening study conducted in Massachusetts detected no cases among 177000 newborn infants.[84] The third disorder, galactose-4'-epimerase (GALE) deficiency (OMIM database No. 230350), occurs in 2 forms; one form is confined to red blood cells and has no symptoms, and the second form, which is exceedingly rare, is generalized, with only a few patients reported nationally.[85,86]

Clinical Manifestations

Infants with classic galactosemia, or GALT deficiency, generally present within the first weeks after birth with a life-threatening illness. Feeding intolerance, vomiting and diarrhea, jaundice, hepatomegaly, lethargy, hypotonia, and excessive bleeding after venipuncture are characteristic findings. Laboratory studies indicate liver and renal tubular disease. Septicemia, particularly with *Escherichia coli*, is not uncommon. Cataracts are generally seen at presentation, but they may be mild in the first few weeks of life and only detectable with slit-lamp examination. Less frequently, patients with classic galactosemia may have a more chronic presentation, with failure to thrive, poor feeding, and developmental delay. Black individuals with classic galactosemia, in particular, frequently have a mild presentation.

Infants with GALK deficiency generally present with bilateral cataracts, which have been observed as early as 4 weeks of age. The cataracts are identical to those seen in classic galactosemia.[87] The great majority of infants with GALE deficiency have an enzyme deficiency that is confined to the red blood cells and causes no symptoms. Five individuals with generalized GALE deficiency had

developmental delay, hypotonia, and poor growth; 3 had sensorineural hearing loss.[88]

Pathophysiology

The main metabolic pathway for the conversion of galactose to glucose uses 3 enzymes: GALK, GALT, and GALE. Individuals who lack GALK cannot convert galactose to galactose 1-phosphate. As a result, galactose is converted to galactitol by an alternative pathway. The accumulation of galactitol in the lens results in the development of cataracts. Individuals with classic galactosemia, or GALT deficiency, cannot convert galactose 1-phosphate to uridine diphosphate galactose. Galactose, galactitol, galactose 1-phosphate, and other metabolites accumulate. Although it seems clear that increased galactitol is responsible for the development of cataracts in all forms of galactosemia, it is not known which metabolites are responsible for the other clinical findings in classic galactosemia.[89]

Inheritance

All forms of galactosemia are autosomal recessive in inheritance. More than 150 different mutations have been identified in GALT, the enzyme that is deficient in classic galactosemia. The most common GALT mutation in Europe and North America is Q188R, which is associated with the severe presentation of classic galactosemia. A mutation found in black and some Hispanic individuals is S135L.[90] This mutation is associated with a milder presentation of the disorder.

Benefits of Newborn Screening

Exclusion of galactose from the diet results in marked improvement of the life-threatening complications of classic galactosemia. However, this treatment has only limited efficacy in the prevention of long-term complications. These include impaired cognitive development, with mean IQ in the range of 70 to 90; verbal dyspraxia, a speech disorder attributable to a sensorimotor disturbance of articulation; growth delay, with ultimate height in the normal range; neurologic findings, including tremor and ataxia beginning in midchildhood to middle age; and ovarian failure, manifesting as delayed puberty, primary amenorrhea, secondary amenorrhea, or oligomenorrhea.[91] Prepubertal children with GALT deficiency are also at increased risk of having decreased bone mineral density despite normal calcium intake.[92]

Screening

Newborn screening for galactosemia may test for galactose, galactose 1-phosphate plus galactose, or GALT enzyme deficiency. Some laboratories test for all of these substances. Because GALT is deficient only in classic galactosemia, this newborn screening test alone will not detect the other 2 forms of galactosemia. The GALT enzyme test has the advantage of being independent of the infant's diet. Therefore, the timing of the newborn screening sample collection will have no effect on the reliability of this test. However, because GALT analysis is performed using red blood cells, there may be a false-negative result for up to 3 months if the infant has received a blood transfusion. Tests for galactose and galactose 1-phosphate depend on the infant's diet; therefore, it is important to be sure that the infant is receiving galactose-containing formula or breast milk before testing. MS/MS can be used as a technology in screening for galactosemia.[93]

Follow-up and Diagnostic Testing

All newborn infants with positive screening results should be evaluated rapidly by an experienced physician for feeding difficulty, signs of sepsis, jaundice, and hepatomegaly. Untreated classic galactosemia may progress very rapidly to hepatic toxicity, with death resulting from sepsis or bleeding. Immediate restriction of dietary galactose is critical and should not await diagnostic testing. Galactose restriction should be instituted immediately even in the asymptomatic child and should be continued until the extent of enzyme deficiency, if any, is known.

Diagnostic studies for classic galactosemia include quantitative analysis of GALT and red blood cell galactose 1-phosphate. In states where the screening test measures GALT activity, these studies will establish or rule out classic galactosemia. When the screening results, including estimates of galactose and galactose 1-phosphate and quantitative GALT activity, are normal, quantitative analysis of GALK and GALE are required to identify these forms of galactosemia. It is likely that another pathway exists that can be responsible for galactose disposal, but this pathway has not been characterized.[94]

Brief Overview of Disease Management

Infants suspected of having galactosemia should be fed with a galactose-free formula until diagnostic testing confirms a specific diagnosis. Children who are seriously ill at the time of diagnosis of classic galactosemia require supportive care, which may include vitamin K supplementation and fresh-frozen plasma transfusions, antibiotics for presumed Gram-negative sepsis, and phototherapy for hyperbilirubinemia. After dietary galactose has been eliminated, most infants improve rapidly. Milk and milk products are excluded from the diet indefinitely, because significant ingestion of galactose at any age can be toxic.[92] Because medications may contain galactose, the pediatrician should instruct parents to ask the pharmacist if a medication is galactose free before administering it to the child. Regular nutritional evaluation is necessary to ensure adequate calcium intake. Regular developmental evaluation and early speech assessment are also required. Girls should be monitored frequently in late childhood and adolescence for pubertal development. Regular measurement of galactose 1-phosphate in red cells is the most common method used to assess dietary compliance.[85]

Lifelong galactose restriction is also indicated for individuals with GALK and generalized GALE deficiencies. No treatment seems to be necessary for red blood cell GALE deficiency.

Current Controversies

In addition to milk products, certain fruits contain significant quantities of galactose.[93] There is no consensus about whether these fruits should be eliminated from the diet, because endogenous synthesis of galactose also occurs.[94] Some authors have suggested that an elemental formula (galactose free) may be preferable to soy formula in the treatment of galactosemia.[95]

Special Issues

Galactose is a reducing substance, and the presence of reducing substances in the urine is sometimes suggested as a test for galactosemia. However, this test is neither sensitive nor specific, and it should not be used as a screening or diagnostic test for galactosemia.

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