

Galactosemia

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Outcome without screening:

Classical galactosemia is a life threatening disorder. Symptoms of classical galactosemia appear soon after ingesting a lactose-based formula or breast milk and include: vomiting, rapid weight loss, hepatomegaly and jaundice. Excess amounts of a galactose metabolite, galactose-1-phosphate, inhibit the conversion of glycogen to glucose which can result in hypoglycemia and seizures. In untreated cases, cataracts result from the accumulation of galactitol, cirrhosis of the liver develops and irreversible brain damage occurs. Many infants die during the first week of life due to liver failure, severe hypoglycemia and/or sepsis (approximately 30% develop gram negative sepsis, often *E.coli*).

Incidence:

The incidence of classical galactosemia is estimated as 1 in 50,000 in the USA and ranges from 1 in 26,000 in Ireland to 1 in 600,000 in Japan. It is more frequent in Caucasians and less frequent in other ethnic groups.

Outcome with screening:

Since classical galactosemia is a life threatening disorder, it is essential that the diagnosis be confirmed and treatment started as soon possible after the results of the first screening test are available. The serious complications of this disease can be prevented by adequate treatment. However, other symptoms such as speech and language delay and ovarian insufficiency may occur in treated cases for reasons that are not yet known.

Causes of galactosemia:

Galactosemia is an inherited autosomal-recessive disorder of galactose metabolism. People with galactosemia cannot tolerate any form of milk (human or otherwise). The sugar lactose (a disaccharide present in milk) is made up of equal parts of glucose and galactose; thus a deficiency of the enzymes involved in galactose metabolism can lead to severe clinical consequences. Ingestion of milk produces toxic levels of galactose and its metabolite galactose-1-phosphate (gal-1-P) in the infant. The classical and most severe form is caused by a deficiency of the enzyme *galactose-1-phosphate uridylyl transferase* (GALT).

Two other enzyme deficiencies also cause galactosemia, one is *epimerase* and the other is *galactokinase*. In cases with a deficiency of one of these enzymes the initial newborn screen will show elevated galactose level with normal GALT enzyme activity. This incongruent result would suggest the possibility of one of the other enzyme deficiencies. Children with galactosemia due to deficiency of these other enzymes may not become as severely ill as the infants with classical galactosemia. However, they may be mentally retarded or have cataracts if not treated. The incidence of these disorders is significantly lower than GALT related galactosemia.

Screening tests and confirmation:

The screening test provided by the Tennessee Newborn Screening Program analyzes the level of galactose and gal-1-P in the blood spot. If the level of galactose/gal-1-P is greater than the normal cut off value of approximately 5, enzyme (GALT) activity is measured. These values are

reported to the physician of record and to the designated Genetic/Metabolic Center. The physician is requested to contact the designated Metabolic Center for assistance in the follow-up testing.

Depending on the level of galactose/gal-1-P, the enzyme activity, and the clinical and feeding status of the infant, the Metabolic Center may recommend a simple repeat of the newborn screening analysis. However, if the specialists suspect the possibility of variant or classical galactosemia they will recommend diagnostic testing. Analysis of red cell gal-1-P, GALT enzyme activity, and electrophoresis to determine enzyme genotype are required to definitively identify classical or variant forms of galactosemia. These tests may take up to a week to complete. Thus, the Metabolic Center may recommend dietary therapy be instituted before the results of these tests have been received.

Treatment:

The treatment consists of a diet with restriction of lactose containing foods and should be continued for life. However, even on a lactose free diet, patients can still have persistent, high levels of urinary galactitol and plasma gal-1-P, due to the presence of galactose in foods other than milk. Galactose is present in many fruits and vegetables, thus a completely galactose free diet is not possible. In addition a certain amount of galactose is required for proper functioning of many physiological processes, thus the body can make some galactose from other sugars.

When notified of a positive galactosemia screen the physician should see the baby immediately. Symptoms (feeding intolerance and weight loss) and signs (dehydration, jaundice, hepatomegaly, sepsis or hypoglycemia) should be taken very seriously. Transfusion may be necessary to reverse the toxic effects in a severely affected infant. Abnormal liver function tests, aminoaciduria, and coagulation defects are common. Urine reducing substance will not be positive unless the galactose and gal-1-P have reached toxic levels. Immediate institution of a lactose free diet (Isomil, Prosobee, Nutramigen or Lactofree) can reverse the acute neonatal symptoms and prevent many of the sequelae (mental retardation, irreversible cataracts, and liver disease). It is important to understand that clearance of galactose and gal-1-P from the circulation is slow. Thus the infant will continue to be at risk for the more severe, acute symptoms for up to 7 days post dietary change.

If a diagnosis of classical galactosemia is established, the infant must be monitored closely for the first weeks and then regularly for the following months for nutritional balance, gal-1-P levels and developmental milestones. Regular consultation with a nutritionist experienced in the nuances of lifelong treatment for this disorder is required.

Special concerns and issues:

Caution in the interpretation of the galactosemia screening and diagnostic studies is required when the baby has received a blood transfusion prior to the test. The transferase enzyme resides in the red cells and the presence of transfused normal red cells with normal levels of transferase may result in detection of intermediate galactose and enzyme values in an infant with classical galactosemia that still needs treatment to prevent symptoms that will develop after the donor red cells are no longer viable. Also, infants given a soybean-based formula before the newborn screening sample is collected may show normal galactose values and enzyme studies are needed to detect the presence of the enzyme deficiency causing galactosemia.

Abnormal results in the neonatal screen for galactosemia are also found when the infant has

one of the mild forms of galactosemia, usually the *Duarte galactosemia variant*. In most of these cases the initial screen shows mild elevation of the galactose values and intermediate enzyme activity. These infants will be asymptomatic. A repeat screen is recommended. If the second test shows similar abnormal results, a confirmatory test is performed. Infants with variants of galactosemia are treated for the first six months to one year of life to prevent mild developmental delay and/or behavior problems that might occur in the absence of treatment. The incidence of variants is 10 times that of classical galactosemia.