Galactosaemia

Synonyms: galactose-1-phosphate uridyltransferase deficiency, GALT deficiency, GALT, galactose diabetes

Although it is a rare inherited disease it is among the most common carbohydrate metabolism disorders. It can be a life-threatening illness during the newborn period. [1] The cardinal features are hepatomegaly, cataracts, and mental handicap. It is caused by mutation in the galactose-1-phosphate uridyltransferase (GALT) gene on chromosome 9 at 9p13. [2]

Pathophysiology[1]

The disease can be variable in terms of severity with a Duarte variant that is comparatively benign. [3] Those who are homozygous for the Duarte variant still have enzyme levels that are about 50% of normal. There are many variants of the disease but most affect one of three enzymes.

- GALT deficiency is the most common abnormality. The enzyme converts galactose-1-phosphate and uridine diphosphate (UDP) glucose to UDP galactose and glucose-1-phosphate. Patients with GALT deficiency have abnormal galactose tolerance.
- Galactokinase converts galactose to galactose-1-phosphate and deficiency is rather more uncommon.
- UDP galactose-4-epimerase epimerises UDP galactose to UDP glucose and deficiency is also less common.

Hypergalactosaemia is associated with these enzyme deficiencies and it is the toxic effects of this that produce the characteristic features of the disease.

Epidemiology

Galactosaemia (galactosemia in USA literature) is an autosomal recessive inherited condition. [2] The incidence of classical galactosaemia in white Americans is around 1 in 47,000. [4]

Presentation [2, 3, 5]

This may be rather variable and not all features listed below will be found. It almost invariably presents in the neonatal period. Variant disease can present later in life.

- There is often feeding difficulty, with vomiting and failure to gain weight, with poor growth in the first few weeks of life.
- Lethargy and hypotonia occur.
- Jaundice and hepatomegaly develop.
- There are often associated coagulation defects.
- Sepsis (often with *Escherichia coli*) can be fatal.
- Cataracts may be apparent even in the early days of life.
- Ascites may even be apparent in early life.
- The fontanelle is full.
- Developmental delay may affect speech, language, and general learning.
- Adults may have short stature, ataxia, and/or tremor.
- Hypergonadotrophic hypogonadism is common and in women, premature ovarian failure. Those who conceive often have variant disease.

Galactosaemia should be considered when a term infant gets an *E. coli* sepsis and when a neonate develops cataracts. It should also be considered with neonatal jaundice and haemorrhage.

Differential diagnosis

- Fructose-1-phosphate aldolase deficiency (fructose intolerance).
- Galactokinase deficiency.
- Hereditary haemochromatosis.
- Alpha-1-antitrypsin deficiency.
- Sepsis.
- Tyrosinaemia.

Investigations[6]
• If the child is having milk, and hence lactose that will be split to glucose and galactose, there will be galactose in the urine. This is a reducing sugar and so gives a positive test with Fehling’s or Benedict’s reagent but a negative test with glucose oxidase test strips. Galactose may appear in the urine of any patient with liver disease and in galactosaemia it can swiftly disappear.
• LFTs should be performed. Hyperbilirubinaemia is often unconjugated at first but becomes conjugated later. Fatty infiltration and inflammatory changes may occur in the liver early on. Portal hypertension and pseudocirrhosis formation develop later. Cirrhosis in the final stage is indistinguishable from other causes.
• There is albuminuria and, later, a generalised aminoaciduria. Eliminating lactose from the diet removes the albuminuria. Amino acids are raised in the blood and raised phenylalanine may give a false positive test for phenylketonuria.
• There is a metabolic acidosis.
• Haemolytic anaemia may occur.
• If there is doubt about cataracts, slit-lamp examination by an ophthalmologist may be required. It should be performed as a routine screening test every six months until the age of 3 and annually thereafter.
• Beutler’s test involves a fluorescent spot test for GALT activity. It is now widely used for the diagnosis of galactosaemia but will give false positives with glucose-6-phosphate dehydrogenase deficiency.
• A quantitative erythrocyte analysis for GALT is required.
• A GALT isoelectric-focusing electrophoresis test helps distinguish variant forms such as the Duarte defect. GALT genotyping may provide a specific molecular diagnosis if available. About 60% of British patients with galactosaemia are homozygous for the Q188R mutation.

Management[3, 7]

• As soon as the diagnosis is made, milk should be discontinued to remove the lactose load. This will have some immediate benefit but will not halt all aspects of the disease. If an infant is to be fed without milk, the advice of a dietician should be sought. A certain amount of galactose is present even in fruit and vegetables and so total elimination is very difficult. As the patient matures, the ability to tolerate lactose improves but milk should be restricted throughout life.
• Milk substitutes can be prescribed on an FP10 prescription and endorsed Advisory Committee on Borderline Substances (ACBS).
• Antibiotics, intravenous fluids and vitamin K are often required.
• Referral should be made to a clinical geneticist to confirm the diagnosis and give counselling to the parents.
• Developmental delay will benefit from special attention to education and schooling. The help of speech and language therapy may be required as the problems of speech appear to be greater than would be expected merely from the reduced intelligence.
• The aetiology of short stature is not understood and there is no known treatment.
• The help of an endocrinologist may be required with hypergonadotrophic hypogonadism. Fertility is unlikely. With premature ovarian failure the use of HRT to prevent osteoporosis should be considered and androgen deficiency may well merit attention in men; however, the risk of hypogonadism in men with the condition is much less than in affected women.
• Puberty in girls may be induced by supervised gradual introduction of ethinylestradiol before moving to a low-dose combined oral contraceptive.
• Sepsis and liver disease are treated as in any other situation. It is important to make the diagnosis early to implement lactose avoidance to reduce long-term problems before such conditions as cirrhosis and cataracts develop; however, most patients will still develop at least one major complication.
• If a woman with galactosaemia does become pregnant, the high level of galactose does not seem to have an adverse effect on the fetus. This is in contrast to the situation with phenylketonuria where the diet must be strictly observed in pregnancy.

Prognosis

Early diagnosis and treatment with a galactose-restricted diet can partially prevent and improve some complications but not all of them. Early diagnosis seems important in the prevention of severe cataracts.[8]

Screening

Prenatal screening is possible. Screening for galactosaemia in neonates is currently not recommended in the UK.[9]

Further reading & references

2. Galactosemia; Online Mendelian Inheritance in Man (OMIM).
5. Berry GT; Classic Galactosemia and Clinical Variant Galactosemia. 2000 Feb 4 [Updated 2014 Apr 3].
9. UK Screening Programmes; UK Screening Portal

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