Galactosaemia: diagnosis, management and long-term outcome

A Broomfield

C Brain

S Grunewald

Abstract

Classical galactosaemia (OMIM 230400) is an inherited disorder of galactose metabolism. The toxic potential of ingested galactose (derived predominantly from lactose) and build-up of intermediates was recognised over 100 years ago. The most common and most severe form is classical galactosaemia, resulting from galactose-1-phosphate uridyl transferase deficiency (GALT). In the UK, patients are usually diagnosed only after they become symptomatic — galactosaemia is not included in the newborn screening programme. Treatment is based on restriction of galactose in the diet, mainly by excluding lactose which is found in milk, milk products and manufactured foods containing milk. Early diagnosis is crucial to prevent acute life threatening complications. Long-term outcome in classical galactosaemia in the overall patients' population remains disappointing. This review gives a summary of current practises, updated recommendations and highlights potential disease burden.

Keywords galactitol; galactosaemia; galactose-1-phosphate; genetic; inherited metabolic disease; Leloir pathway

Definition

Galactosaemia results from a defect in the galactose metabolic pathway, the so-called Leloir pathway, which consist of three enzymes, the galactose specific kinase (Galactokinase/GALK), galactose-1-Phosphate uridyltransferase (GALT) and uridine diphosphate galactose-4-epimerase (GALE). Whilst a deficiency in any of these enzymes will lead to the biochemical finding of galactosaemia i.e. an elevated plasma galactose, only deficiencies in GALT or GALE have the potential to cause the 'classical Galactosaemia' phenotype: an acute toxicity syndrome which resolves on removal of exogenous galactose intake. However, even on an appropriate diet, long-term complications including neurological, neuropsychological, endocrine and bone problems have been reported.

Abbreviations: GALT, galactose-1-phosphate uridyltransferase; GALK, galactokinase; GALE, galactose 4-'epimerase; GAL-1-P, galactose-1-phosphate.

A Broomfield *MD is a Consultant in Willink Biochemical Genetics Unit, St. Mary's Hospital, Manchester, UK.*

C Brain *MD is a Consultant Paediatric Endocrinologist in the Endocrine Department, Great Ormond Street Hospital for Children, London, UK.*

S Grunewald *MD PhD is a Consultant in Paediatric Metabolism, Metabolic Medicine Unit, Great Ormond Street Hospital for Children with UCL Institute of Child Health, London, UK.*

Incidence/genetics

The overall incidence of classical galactosaemia, secondary to GALT deficiency is estimated as 1: 25,000 to 1: 44,000 in the UK, which is in keeping with most of Western Europe. The incidence in different subpopulations varies greatly, quoted as 1 in 50,000 in the USA and as little as 1 in 100,000 in Japan. In Ireland, the incidence in the travelling population is as high as 1 in 450 live births. The incidence of the less severe compound heterozygote form, so called Duarte galactosaemia, is 1:4000—5000.

The mild asymptomatic phenotype of GALE is relatively common, with a frequency of 1: 6200 in the African American population. The severe phenotypes of GALE, presenting similar to classical galactosaemia has been reported in a few case studies worldwide. The GALK deficiency is very rare with an incidence of $<1/100{,}000$.

The GALT gene is located on chromosome 9p13 and consists of 11 exons. Over 230 mutations have been described. The most frequent mutation in the Caucasian population, with an overall frequency of 65% (but 96% in the Irish population), is the Q188R mutation, resulting in a complete loss of enzymatic activity and being predicative of a poorer clinical outcome. The second commonest European mutation is the K285N, a missense mutation, which predominates in central European countries. This also results in a complete lack of GALT activity. S135L, accounting for about 50% of mutate alleles in the African American population, is associated with the milder phenotype seen in Afro-Caribbean patients. The N314D mutation (c. 940A > G), so called Duarte variant can exist in two different forms: Duarte-1 and Duarte-2 and is predicted to lead to a favourable clinical outcome. Compound heterozygocity for the Duarte-2 variant and classical galactosaemia mutation typically manifest in 14—25% of normal GALT activity resulting in some protection against severe toxicity.

Pathology

Goppert first described the disease in 1917 and Isserbacher and colleagues revealed the underlying enzyme defect of classical galactosaemia in 1956. The three different metabolic conditions in the galactose metabolic pathway, known as the Leloir pathway, relate to three enzymes: galactose specific kinase (Galactokinase/GALK), galactose-1-Phosphate uridyltransferase (GALT) and Uridine diphosphate galactose-4-epimerase (GALE). Any disruption of the Leloir pathway, potentially results in an excess of galactose accumulation, which if uncontrolled will also result in accumulation of galactitol and galactonate as a result of activation of alternative pathways of galactose metabolism i.e. aldose reductase and the pentose phosphate pathway respectively (Figure 1).

Given that the GALK deficient patients do not manifest either the acute toxicity, or any of the chronic manifestations seen in GALT patients, it seems likely that Galactose-1-Phosphate which is absent in GALK but present in GALT, plays a major role in their pathogenesis. The accumulation of galactitol is thought to be responsible for the cataracts seen, though whether this is due to direct osmotic effects or due to oxidative damage secondary to NADPH depletion is unclear. It is also unclear if galactonate, cleared by the pentose 5 phosphate pathway, contributes to the overall toxicity.

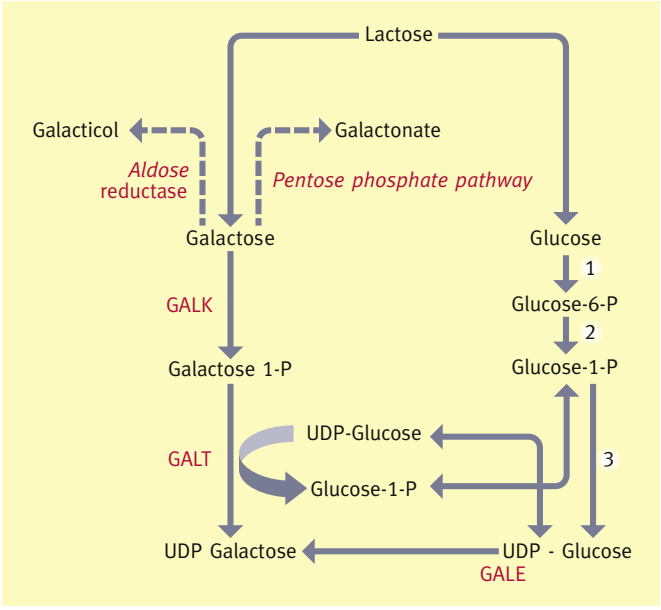

Figure 1 The Leloir pathway and alternative pathways for galactose metabolism (dotted lines).1 = hexokinase, 2 = phosphoglucomutase, 3 = UDP-glucose pyrophosphorylase.

The enzymes involved in the Leloir pathway ultimately control the levels of UDP-galactose, the galactosyl donor in cellular glycoprotein/glycolipid biosynthesis. This potentially leads to abnormalities in post translational protein modification. Abnormal glycosylation has been demonstrated in several N-glycosylated glycoproteins such as FSH, transferrin or IgG, comparable with changes seen in patients with congenital disorders of glycosylation (CDG).

The most apparent effect on a secondary pathway is the reduction in levels of cellular inositol, with reductions in myo-inositol being documented *in vivo*. GAL-1-P competitively inhibits human inositol monophosphatase and in the yeast model, galactose toxicity can be overcome by over-expression of inositol monophosphatase. The reduction in inositol might partially explain some of the neurological symptoms seen in galactosaemic patients since inositol is required for the formation of the neuronal modulator phosphatidylinositol bisphosphate.

The clinical symptoms of acute toxicity syndrome of classical galactosaemia

Classical galactosaemia is potentially an acute, toxic, life threatening disease and early diagnosis is essential to reduce morbidity and mortality. Acute toxic effects result in weight loss, faltering growth, severe liver impairment and susceptibility to *Escherichia coli* sepsis. Supportive treatment (intravenous fluids, antibiotics, plasma and/or Vitamin K supplementation) might be required. Symptoms of liver dysfunction evolve as early as day one but milder phenotypes can present after several weeks of age. Nonetheless, early acute onset is the norm with about 80% of patients presenting in the first 2 months of life in one large cohort study.

Examination on presentation may reveal signs of liver impairment such as jaundice, hepatomegaly and signs of bleeding; as well as occasional fullness of the anterior fontanelle either due to sepsis or pseudotumour cerebri. Whilst cataracts are a recognized feature of GALT deficiency, outside of the MRCPCH examination they are not a particularly common clinical feature with only 14% of patients being affected in larger, contemporary case series. Even when present, they may require the use of a slit lamp for visualization. Cataracts are the only notable complication in GALK deficiency, though very rarely pseudotumour cerebri has also been reported. GALE presentation is variable: ranging from isolated asymptomatic hypergalactosaemia, to the severe classical galactosaemia type clinical picture.

Differential diagnosis and confirmation of the diagnosis

There are few causes of galactosaemia other than Leloir pathway defects, however, any significant liver dysfunction has the potential to decrease hepatic galactose handling; leading to a 'secondary galactosaemia'.

The differential diagnosis for neonatal liver dysfunction is far wider, with very variable pathogenesis, such as infections, structural abnormalities e.g. biliary atresia or other inborn error of metabolism (IEM). Thus any child with acute liver dysfunction in the neonatal period should be thoroughly investigated both biochemically and radiologically as treatment of those different diagnosis vary. Of the IEM, urea cycle disorders, fatty acid oxidation disorders and organic acidemias can present with impairment in liver function. The inborn error that most closely mirrors galactosaemia's presentation is tyrosinaemia type I, which also presents in the neonatal period with acute liver and renal tubular dysfunction. The investigations listed in Table 1, whilst not an exhaustive list, are designed to exclude most of the more common causes.

The diagnosis of GALT deficiency can be confirmed by measuring the GAL-1- PUT activity either by the Beutler fluorescent spot test or quantitative assay of red blood cell galactose-1-phosphate uridyl transferase activity. The later, though more labour intensive, has the advantage of being able to distinguish variants with residual activity. Both assays are erythrocyte based and invalidated by recent blood transfusions, though quantitative assays of both parents can be informative in these circumstances, as they can determine potential carrier status. Table 2 gives the specific tests, both screening and confirmatory, for galactosaemia (see Table 3).

Management

The initial management of classical galactosaemia is the withdrawal of both exogenous galactose and lactose (which is broken down to glucose and galactose *in vivo* – Figure 1) from the diet. All unmodified mammalian milk contains lactose therefore withdrawal of breast feeding or standard infant formula should be instituted immediately once galactosaemia is considered.

Suitable milk substitutes are either soya based infant formulas (e.g. Cow and Gate Infasoy, SMA Wysoy), or in patients with a degree of acute hepatic dysfunction and possibly limited absorption, casein hydrolysate infant formulas such as Pregestimil or Nutramigen (these contain only very small amounts of galactose) or amino acid based infant formulas such as Nutramigen AA or Neocate LCP. To improve the severe liver dysfunction, administration of vitamin K might be necessary and neonates that cannot be fed should be given at least 6 mg/kg/