Classical galactosaemia revisited

Annet M. Bosch

Summary Classical galactosaemia (McKusick 230400) is an autosomal recessive disorder of galactose metabolism, caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT; EC 2.7.712). Most patients present in the neonatal period, after ingestion of galactose, with jaundice, hepatosplenomegaly, hepatocellular insufficiency, food intolerance, hypoglycaemia, renal tubular dysfunction, muscle hypotonia, sepsis and cataract. The gold standard for diagnosis of classical galactosaemia is measurement of GALT activity in erythrocytes. Gas-chromatographic determination of urinary sugars and sugar alcohols demonstrates elevated concentrations of galactose and galactitol. The only therapy for patients with classical galactosaemia is a galactose-restricted diet, and initially all galactose must be removed from the diet as soon as the diagnosis is suspected. After the neonatal period, a lactose-free diet is advised in most countries, without restriction of galactose-containing fruit and vegetables. In spite of the strict diet, long-term complications such as retarded mental development, verbal dyspraxia, motor abnormalities and hypergonadotrophic hypogonadism are frequently seen in patients with classical galactosaemia. It has been suggested that these complications may result from endogenous galactose synthesis or from abnormal galactosylation. Novel therapeutic strategies, aiming at the prevention of galactose 1-phosphate production, should be developed. In the meantime, the follow-up protocol for patients with GALT deficiency should focus on early detection, evaluation and, if possible, early intervention in problems of motor, speech and cognitive development.

Abbreviations

EGS endogenous galactose synthesis
FSH follicle-stimulating hormone
Gal-1-P galactose 1-phosphate
GALE UDP-galactose epimerase
GALK galactokinase
GALM galactose mutarotase
GALP galactose-1-phosphatase
GALT galactose-1-phosphate uridyltransferase
HRQoL Health Related Quality of Life

Introduction

Classical galactosaemia (OMIM 230400) is an autosomal recessive disorder of galactose metabolism caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT; EC 2.7.712). The incidence in Western Europe has been estimated to be between 1:23,000 and 1:44,000 (Bosch et al 2005; Honeyman et al 1993; Schweitzer-Krantz 2003). Most patients present in the neonatal period, after ingestion of galactose-containing feeds, with jaundice, hepatosplenomegaly, hepatocellular insufficiency, food intolerance, hypoglycaemia, renal tubular dysfunction, muscle hypotonia, sepsis and cataract. Treatment, consisting of a
severe restriction of dietary galactose, is life-saving (Holton et al 2001). For many years, elimination of galactose from the diet was considered to be an effective therapy to prevent complications. However, long-term follow-up of patients with classical galactosaemia has shown that, despite a strict diet, most patients develop symptoms such as retarded mental development, verbal dyspraxia, motor abnormalities and hypergonadotrophic hypogonadism (Kaufman et al 1981, 1995; Komrower and Lee 1970; Levy et al 1994; Nelson 1995; Ridel et al 2005; Schweitzer et al 1993; Segal 1998; Waggoner et al 1990). Endogenous production of galactose, amounting to 1 gram per day in adults, has been suggested to be a major cause of the late complications (Berry et al 1995; Schadewaldt et al 2004a).

**Galactose metabolism**

In the human body, most of the ingested galactose is rapidly metabolized to glucose 1-phosphate by the action of four consecutive enzymes (Holden et al 2003): galactose mutarotase (GALM), galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), and UDP-galactose mutarotase (GALM), galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), and UDP-galactose epimerase (GALE). These enzymes allow the subsequent conversion of β-D-galactose into α-D-galactose (GALK), of α-D-galactose into galactose 1-phosphate (GALK), of galactose 1-phosphate and uridine diphosphate-glucose (UDP-glucose) into glucose 1-phosphate and UDP-galactose (GALT), and the interconversion of UDP-glucose and UDP-galactose (GALE) (Fig. 1). These enzymes constitute the Leloir pathway, named after one of the major contributors to the identification of this pathway in yeast and bacteria. Mutations in each of the genes coding for the three last enzymes of the Leloir pathway may cause a major decrease in enzyme activity, resulting in variable clinical phenotypes. Of these three types of galactosaemia, GALT deficiency is by far the most prevalent, and is called classical galactosaemia (OMIM 230400).

Enzymes of the Leloir pathway are present in many tissues and cell types in the body including the erythrocyte. Besides the Leloir pathway, three accessory pathways for galactose metabolism have been described.

The pyrophosphorylase pathway was first speculated upon by Isselbacher in 1957. This pathway involves a reversible UTP-dependent pyrophosphorylase reaction converting galactose 1-phosphate into UDP-galactose and can metabolize galactose at a rate of only 1% of that of the Leloir pathway. The activity of the pyrophosphorylase pathway increases with age in most tissues. Activity is highest in adult liver, amounting to about 5% of the liver GALT activity (Shin et al 1987). Probably the most important function of the pyrophosphorylase pathway is the generation of UDP-galactose and UDP-glucose for incorporation into glycoproteins and glycolipids.

The second accessory pathway is catalysed by the enzyme aldose reductase, reducing galactose to galactitol. As galactitol cannot be further metabolized by sorbitol dehydrogenase, it is excreted in the urine. However, galactitol can also accumulate in tissues, probably contributing to the development of both the cataract and the pseudotumor cerebri observed in classical galactosaemia.

A third metabolic route is revealed by the observation that patients with classical galactosaemia produce galactonate from galactose and excrete it in the urine (Cuatrecasas and Segal 1996; Wehrli et al 1997). The exact metabolic mechanism of the production of galactonate remains unclear. Further proof for the existence of one or more alternative pathways for galactose oxidation has come from a study demonstrating galactose oxidation in a patient homozygous for a large deletion in the GALT gene (Berry et al 2001).

**Molecular biology**

Classical galactosaemia is inherited as an autosomal recessive disorder and the gene encoding GALT is located on chromosome 9p13 and spans 4.3 kb of DNA arranged into 11 exons. It was cloned in 1992 by Leslie and colleagues, and over 180 different mutations have been identified (Tyfield and Carmichael, GALTdb: http://www.ich.bris.ac.uk/galtdb).

The most common mutation in classical galactosaemia is the p.Q188R mutation, changing the glutamine at position 188 into arginine. It is the most frequent mutation in all caucasian populations, with the highest frequency (65%) in Western Europe (Tyfield et al 1999). The p.S135L mutation (replacing serine with leucine) is found almost exclusively in the African American population and is the most frequently reported mutation (50%) in this population (Lai et al 1996). Neither the p.Q188R nor the p.S135L mutation was detected in Japan, where the incidence of classical galactosaemia is very low (1:1 000 000). Ten mutations, not reported in caucasians, were detected in 15 Japanese patients with classical galactosaemia (Hirokawa et al 1999). The p.N314D mutation, however, occurs in caucasians and Asians as well as African Americans (Tyfield et al 1999). The differences in frequency and spectrum of mutations in the different populations suggest the occurrence of a few very ancient mutations such as p.N314D, with most other mutations occurring after racial divergence (Novelli and Reichardt 2000).

Previously, the p.N314D allele was thought to give rise to two clinically relevant GALT enzyme variants, as it was associated with an increased enzyme activity in some (Los Angeles type, D1) and a reduced enzyme activity in others (Duarte type, D2) (Elsas et al 1994; Podskarbi et al 1996). In the Los Angeles type, the p.N314D mutation is coupled with a polymorphic variant, p.L218L, which has been speculated to