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EDITORIAL

Classic galactosemia: dietary dilemmas

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Introduction

Classic galactosemia (McKusic 230400) is an inborn error of galactose metabolism caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT, EC 2..7.712), resulting in accumulation of the metabolites galactitol and galactose-1-phosphate. Patients ingesting galactose from breast milk or infant formula present in the first weeks of life with feeding difficulties, hepatocellular dysfunction, hypoglycemia, renal tubular dysfunction, cataract, and sepsis. Immediate removal of galactose from the diet results in a full recovery from this life-threatening neonatal crisis (Holton et al. 2001; Bosch 2006).

Mason and Turner (1935) were the first to report the successful use of a milk-free diet in an infant with galactosemia. In the 1950s, different strategies to feed infants a diet without galactose were discussed in the literature (Salt et al. 1955; Jones and Leak 1959). Nowadays, initiating the diet is much easier, as infant formulas with a very limited amount of galactose are widely available. Still, there are dilemmas in the treatment of galactosemia, and the dietary treatment varies widely around the world. The most troubling issue is that despite a continued galactose-restricted diet, and irrespective of a neonatal crisis, many patients suffer from long-term complications, such as reduced cognitive ability, language impairment, decreased bone mass, and hypergonadotrophic hypogonadism in women (Kaufman et al. 1981; Waggoner et al. 1990; Schweitzer et al. 1993; Panis et al. 2004; Potter et al. 2008; Schadewaldt et al. 2010).

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Infancy

In the first weeks of life, the most important part of managing patients with classic galactosemia is removing all galactose from the diet as soon as the diagnosis is suspected, immediately after starting the diagnostic investigations and without awaiting results, in order to prevent further life-threatening complications. Whereas classic galactosemia is part of the newborn screening programs of many countries, most children will present with clinical symptoms, such as feeding problems, jaundice progressing to liver failure, and sepsis, before the screening results are available. Infants with classic galactosemia must be prescribed a galactose-free formula. In The Netherlands, the recommended treatment is soy milk; in some other countries, infant formula on the basis of casein hydrolysate and dextrine maltose as carbohydrate source, such as Nutramigen®, is recommended. The safety of long-term use of soy milk has been much debated; however, there is no clinical evidence for harmful effects of this product (Merritt and Jenks 2004; Turck 2007). Both Nutramigen and soy formula still contain very small amounts of galactose, and recent studies demonstrated that completely eliminating galactose from the diet by prescribing an elemental formula (Neocate®) instead of Nutramigen® or soy formula caused a significantly faster decrease of the high erythrocyte Gal-1-P values that are found in infancy in these patients (Ficicioglu et al. 2005; Zlatunich and Packman 2008). As the time of diagnosis and

the occurrence of the neonatal crisis do not seem to have a significant effect on long-term outcome, it remains to be elucidated whether this rapid decrease would positively affect outcome, and long-term studies need to be performed to clarify this before routinely putting these infants on this expensive and unpalatable formula (Schweitzer-Krantz 2003).

Childhood

With the introduction of solid foods, some galactose will inevitably be introduced into the diet, as many foods, such as fruit and vegetables, bread, legumes, and offal, contain trace amounts of galactose (Gross and Acosta 1991; Acosta and Gross 1995). Bound galactose is found in many vegetables as part of raffinose and stachyose. How much of this bound galactose can be broken down in the gut is not known. No significant contribution to the intake of galactose, or effect on biochemical parameters, has been demonstrated (Wiesmann et al. 1995).

There are major controversies concerning the daily allowance of galactose during long-term treatment. Many European metabolic centers recommend a very strict diet, also restricting galactose containing fruits and vegetables. Other centers, e.g., in the UK, Germany, The Netherlands, and the USA, are more liberal, advising only a lactose-free diet. There is limited knowledge of the tolerance for exogenous galactose in patients with classic galactosemia. A newborn infant with galactosemia ingesting 300 ml of formula or breast milk per day in the first days of life, equivalent to >7,000 mg of galactose, will develop severe illness. As soon as the diagnosis is suspected, the galactose intake will be restricted as much as possible. Patients on a lactose-free diet with no restrictions of fruit and vegetables will have a daily intake of galactose <30 mg (Berry et al. 1993; Bosch et al. 2004a). On a diet enriched in fruit and vegetables, this intake increases to an average of 54 mg of galactose per day (Berry et al. 1993). In one study, three adolescents ingested up to 600 mg of galactose per day for 6 weeks without any effect on clinical or laboratory parameters (Bosch et al. 2004a). Of importance is the strong contrast between the exogenous intake of galactose in the lactose-restricted diet, with an average intake of 54 mg of galactose per day with a diet enriched in galactose-containing fruit and vegetables and the endogenous production of galactose in adult patients, amounting to 1,000 mg per day (Berry et al. 2004, Huidekoper et al. 2005). This fact is an argument not to restrict fruit and vegetables from the diet. Also, after the introduction of a less restricted diet in Australia, no increases in gal-1-p values were detected (Thompson et al. 2003). Furthermore, in the UK, where fruit and vegetables are not restricted from the diet, no new cataracts or liver diseases have been reported in the literature. It has been demonstrated that the endogenous production of galactose is not affected by the exogenous intake from the diet. (Huidekoper et al. 2005)

Adulthood

There is no insight into galactose tolerance of adults patients with classic galactosemia. Two remarkable patients have been reported in the literature. A 38-year-old adult woman and a 34-year-old man, both with classic galactosemia (Q188R homozygous), had both discontinued their diet at the age of 3 years (Lee et al. 2003; Panis et al. 2006). Her intake of galactose was 2,690 mg per day, and his daily galactose intake was 9,000 mg. In both patients, there were no signs of cataract or liver disease, and red cell galactose-1-phosphate and urine galactitol were within the range of treated galactosemics. The female patient had started hormonal replacement therapy at 15 years of age because of primary amenorrhoea. Her neuropsychological assessment showed a verbal IQ of 88 and a performance IQ of 78; tests of attention, memory, and executive functions were below the tenth percentile for a normal population. The male patient had an unremarkable neurologic examination and a normal educational attainment. His in vivo oxidation of [1-13C] galactose was evaluated and found to be severely hampered and within the range for treated patients. These patients' outcomes seem no worse than in many patients with classic galactosemia treated with a strict diet. It is very well possible that the galactose tolerance of patients with classic galactosemia increases with age as a result of the age-related decrease of endogenous galactose production (Berry et al. 2004; Schadewaldt et al. 2004). It might also be possible that these patients have a greater capacity to dispose of galactose by pathways yet unknown. Alternatively, other factors, such as an aldose reductase deficiency as reported in the galactosemic mouse, may play a role (Ai et al. 2000; Segal 2004). In addition, it is not known whether red cell galactose-1-phosphate or urinary galactitol reflect the long-term toxicity of galactose in galactosemia. Long-term exposure to galactose could result in abnormal galactosylation of glycoproteins and glycolipids, and these patients might well have had an even better cognitive outcome if they had continued their diet.

Future perspectives

Based on the theory that exogenous galactose tolerance increases in adulthood, partly due to the relative decrease in

endogenous production, relaxation of the galactose-restricted diet in adulthood might be considered (Berry et al. 2004; Schadewaldt et al. 2004). A slight relaxation, such as a lactose-restricted diet without limitations in intake in fruit and vegetables can very well be justified in the light of the available evidence and is the standard of care in many countries. Increasing the daily galactose intake from 27 to 54 mg per day is a minor increase when considering the fact that an adult will have an endogenous production up to 1,000 mg per day (Berry et al. 2004; Huidekoper et al. 2005). A further relaxation of the diet, however, will cause a major increase of daily galactose intake. As milk and milk-containing products such as yoghurt contain 2,400 and 1,800 mg of galactose per 100 mg, respectively, the intake of even one glass of milk rapidly increases the daily intake to more than 4,800 mg per day, more than four times the daily endogenous production. Therefore, full dietary relaxation should probably be strongly discouraged until the pathophysiology behind the long-term complications has been elucidated and it is clear whether or not this is related to galactose intake. Long-term studies, preferably after developing a more valid biochemical marker for galactose toxicity, evaluating the biochemical and clinical effects of exogenous galactose in adults as well as in children, are necessary before any further relaxation of the diet can be considered.

Even though a lifelong diet will affect the daily lives of the patients, a lactose-free diet without restriction of fruit and vegetables is a palatable and not very complicated diet. Studies have demonstrated that patients with classic galactosemia have a severely hampered quality of life (Bosch et al. 2004b). However, it has been demonstrated that this is the result of the late complications that are found in many patients and not a result of the diet (Bosch et al. 2009). As the late complications may result from continuous intoxication by galactose from endogenous production, dietary relaxation might well increase the long-term complications by rapidly increasing galactose load and thus affect patients' quality of life even more.

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