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Clinical features of galactokinase deficiency: A review of the literature

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Summary: Galactokinase deficiency (McKusick 230200) is a rare autosomal recessive inborn error of galactose metabolism. Cataract and, rarely, pseudotumor cerebri caused by galactitol accumulation seem to be the only consistently reported abnormalities in this disorder. We performed a literature search to obtain information on the clinical spectrum of galactokinase deficiency. A total of 25 publications were traced describing 55 galactokinase-deficient patients. Cataract was reported in most patients. Clinical abnormalities other than cataract were reported in 15 (35%) out of 43 cases on which information was available. However, all symptoms were reported infrequently and a causal relationship with the galactokinase deficiency is unlikely. As cataract and pseudotumor cerebri appear to be the sole complications of galactokinase deficiency, the outcome for patients with galactokinase deficiency is much better than for patients with classical galactosaemia (McKusick 230400), a more common autosomal recessive disorder of galactose metabolism caused by galactose-1-phosphate uridyltransferase (GALT; EC 2.7.7.12) deficiency. Long-term follow-up of patients with this disorder has shown that, in spite of a severely galactose-restricted diet, most patients develop abnormalities such as a disturbed mental and/or motor development, dyspraxia and hypergonadotropic hypogonadism. Endogenous production of galactose has been considered an important aetiological factor. Although damage may well occur *in utero*, available evidence suggests that damage will continue after birth. Inhibition of galactokinase may then be a promising approach for controlling damage in GALT-deficient patients.

Galactokinase deficiency (McKusick 230200) is a rare autosomal recessive inborn error of galactose metabolism. In the Leloir pathway, galactokinase (EC 2.7.1.6) catalyses the phosphorylation of galactose with ATP to galactose 1-phosphate. The disorder was first described by Gitzelmann (1965, 1967). The estimated incidence varies. Thalhammer and colleagues (1968) reported the first case discovered in a newborn screening programme after screening 35 770 neonates for hypergalactosaemia. Mayes and Guthrie (1968) determined galactokinase activity in a mostly caucasian population and reported an estimated incidence of heterozygotes of 1:107. They concluded that galactokinase deficiency should occur in about 1:40 000 to 1:50 000 births. Levy (1980), however, found only six neonates with galactokinase deficiency after screening 6 000 000 infants for hypergalactosaemia. As a number of the reported patients were of Roma ancestry, the incidence may vary among different populations (Gitzelmann 1965; Kalaydjieva et al 1999; Linneweh et al 1970; Thalhammer et al 1968). Stambolian and colleagues (1995) localized the human galactokinase gene, *GK1*, to the 17q24 region and many private mutations have been reported in galactokinase-deficient patients (Hunter et al 2001; Kolosha et al 2000; Stambolian et al 1995). In Roma patients, a founder mutation (P28T) was reported (Kalaydjieva et al 1999).

Cataract caused by galactitol accumulation seems to be the only consistent abnormality in galactokinase deficiency (Holton et al 2001) and this can be prevented with a galactose-restricted diet. However, other abnormalities have been reported in association with galactokinase deficiency, but it is unclear whether these are a result of galactokinase enzyme deficiency (Segal et al 1979). This relatively benign course of the disease is in strong contrast with high percentage of late complications that have been reported in the more common disorder of galactose metabolism galactose-1-phosphate uridyltransferase (GALT; EC 2.7.7.12) deficiency. Nevertheless, since most cases of galactokinase deficiency have been reported as isolated patients, it is difficult to obtain a good overview of the pathology. We therefore performed a literature search to obtain information on the clinical spectrum of galactokinase deficiency in comparison with classical galactosaemia.

METHOD

A search was done in EBSCO Medline and PubMed with the terms galactokinase deficiency/human. We searched for publications in English, German, French and Dutch. Only 71 publications were retrieved. The abstracts were screened for patient reports. References in Holton and colleagues (2001) were checked and publications not previously found in EBSCO Medline or PubMed were added. Of all retrieved publications containing clinical information, references were carefully checked for additional clinical reports.

RESULTS

A total number of 25 publications were traced, describing 55 galactokinase-deficient patients. In all cases the diagnosis was established by demonstrating deficient activity

of the galactokinase enzyme, usually in erythrocytes. Publications reporting galactokinase variants were excluded. Some patients have been described in more than one publication. Only the publication containing the most clinical information on each patient is included. (Beutler et al 1973; Borzy et al 1984; Colin et al 1976; Cook et al 1971; Dahlqvist et al 1970; Gitzelmann 1965, 1967; Kalaydjieva et al 1999; Kaloud et al 1972; Kerr et al 1971; Kolosha et al 2000; Kurt et al 2002; Levy et al 1972; Linneweh et al 1970; Litman et al 1975; Monteleone et al 1971; Olambiwonnu et al 1974; Pickering and Howel 1972; Segal et al 1979; Sitzmann et al 1977; Stambolian et al 1995; Thalhammer et al 1968; Vecchio et al 1976; Vigneron et al 1970; Xu et al 1989).

The combined results are shown in Table 1. Cataract is a frequent feature in the galactokinase-deficient patients. Only patients detected by neonatal screening did not suffer from cataract. Clinical abnormalities other than cataract were reported in 15 (35%) out of 43 cases on which information was available. Central nervous system abnormalities (mental retardation, neurofibromatosis, neurological deterioration, epilepsy and pseudotumor cerebri) were reported in 8 (19%) out of 43 cases. Mental retardation was described in 3 (7%) out of 43 patients. Two of them are brothers with cataract, mental retardation and severe speech delay, reported by Segal (1979). One patient with mild mental retardation was reported by Kolosha and colleagues (2000). Gitzelmann (1965, 1967; Gitzelmann et al 1974) reported the first galactokinase-deficient patient, a male with galactokinase deficiency and neurofibromatosis. His mother also suffered from neurofibromatosis. His intelligence was normal and his neurological complications were consistent with the neurofibromatosis. Pickering and Howel (1972) described a girl with neurological

Table 1 Family history and symptoms in galactokinase deficiency

Feature	*Number of cases with feature/number of informative cases*	%
Consanguinity	9/35	26
Roma ancestry	11/27	40
Cataract	24/32	75
Mental retardation	3/43	7
Epilepsy	1/43	2
Neurological deterioration	1/43	2
Neurofibromatosis	1/43	2
Pseudotumor cerebri	2/43	5
Asphyxia	1/43	2
Premature birth	1/43	2
Small for gestational age	3/43	7
Failure to thrive	1/43	2
Slow feeding	1/43	2
Hypoglycaemia	1/43	2
Hepatosplenomegaly	2/43	5
C2 complement deficiency	1/43	2

deterioration after developing severe epilepsy from age 17. She was diagnosed with cataract at age 4 and was treated with a diet for a possible GALT deficiency. This girl was later found to have galactokinase deficiency. In two patients with normal psychomotor development aspecific EEG abnormalities were reported (Dahlqvist et al 1970; Kaloud et al 1972). Pseudotumor cerebri was described as a presenting feature in two patients. Both recovered after starting the diet and developed normally (Colin et al 1976; Litman et al 1975).

Prematurity and neonatal asphyxia were mentioned once (Kerr et al 1971; Pickering and Howel 1972). Three children (7%) were small for gestational age; one suffered from failure to thrive (Linneweh et al 1970; Pickering and Howel 1972; Kolosha et al 2000). A transient mild hepatosplenomegaly with normal liver enzymes was reported in two children at the time of diagnosis (Kerr et al 1971; Thalhammer et al 1968). Poor feeding that improved after the start of the galactose-restricted diet was reported in one patient (Dahlqvist et al 1970). Another patient had a single episode of hypoglycaemia (1.8 mmol/L) at the time of diagnosis at 8 weeks of age (Cook et al 1971).

A deficiency of C2 complement was reported in one patient. However, she had a sibling with normal galactokinase activity who also suffered from C2 deficiency. In this patient growth was reported to be below the 5th centile (Borzy et al 1984). Finally, one remarkable patient was reported with galactokinase deficiency in the neonatal period but increasing galactokinase activity with time and normalization after 7 months (Vigneron et al 1970).

DISCUSSION

Other than cataract, no consistent abnormalities were reported in galactokinase-deficient patients. The reported association of neurofibromatosis and C2 deficiency is unlikely to be related to the galactokinase deficiency in these patients. Pseudotumor cerebri has been reported in two patients with galactokinase deficiency (Colin et al 1976; Litman et al 1975) as well as in three patients probably suffering from classic galactosaemia (presenting with galactosuria, jaundice, feeding problems, liver function abnormalities and red blood cells unable to convert galactose to CO_2) (Huttenlocher et al 1970), and resolved completely after starting the diet. The common pathogenic factor in both disorders is the accumulation of galactitol, resulting in osmotic swelling, which is associated with both cataract and pseudotumor cerebri (Wang et al 2001).

The relationship between the galactokinase deficiency and the mental retardation that was reported in three patients is unclear. As the 21-year-old girl (Pickering and Howel 1972) had been on a galactose-restricted diet since 4 years of age, the galactokinase deficiency seems an unlikely cause for her neurological deterioration and severe epilepsy at the age of 17 years. The mental retardation described in the two brothers by Segal and colleagues (1979) is unlikely to be related to the deficiency of galactokinase. Details of the mild retardation reported by Kolosha and colleagues (2000) in a patient are not given in their paper. To our knowledge,

psychomotor retardation has only been described in these three discussed cases and not in any of the other patients. All other symptoms were reported infrequently and a causal relationship with the galactokinase deficiency is highly unlikely. As cataract and, rarely, pseudotumor cerebri appear to be the sole complications of galactokinase deficiency, the outcome for patients with galactokinase deficiency seems to be much better than for patients with classical galactosaemia. The pathogenic factors in classical galactosaemia are not known. In GALT-deficient mice created by Ning and colleagues (2000), galactose 1-phosphate was found to accumulate in liver, kidney and brain, with very high levels of galactose 1-phosphate in red blood cells, comparable to the findings in GALT-deficient humans. Surprisingly, these mice showed no evidence of galactose toxicity. However, the concentrations of galactitol in these GALT-deficient mice were significantly lower than observed in humans. This is probably caused by the low levels of aldose reductase in normal mouse tissues (Ai et al 2000). Possibly it requires the combination of both high levels of galactitol and high levels of galactose 1-phosphate to cause the pathological abnormalities found in classical galactosaemia. Prevention of the formation of galactose 1-phosphate in patients with GALT deficiency might thus prevent late complications. Inhibition of galactokinase activity by a selective inhibitor might be a promising approach for controling damage in GALT-deficient patients. We are therefore trying to develop such selective inhibitors.

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