Galactose intolerance and the risk of cataract

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SUMMARY Cataracts may arise in association with various major and minor disorders restricting galactose metabolism, and the risk is broadly associated with the degree of galactose intolerance. A family is described in which a girl presented at the age of 7 1/4 years with cataracts, galactosuria, and partial deficiencies of the enzymes galactokinase and galactose-1-phosphate uridylic transferase. Galactose intolerance as determined by an oral test was impaired and fluctuated with variation in activity of the above galactose enzymes. Minor defects were also present in the parents and a maternal half-brother. The child has a compound disorder of galactose metabolism differing from those previously described. Assessment of galactose tolerance may be useful in the investigation of families with an incidence of cataract.

Various disorders restricting galactose metabolism may be associated with the development of cataract, apparently via osmotically induced damage consequent to galactikol accumulation within the lens. The association with cataract is very strong for homozygous galactokinase deficiency and moderate for heterozygotes, with expression predominantly and perhaps entirely restricted to the first year of life. The association is also strong for galactosaemia—homozygous galactose-1-phosphate uridylic transferase deficiency—and for some rare variant forms associated with considerable reduction in the activity of this enzyme. Heterozygotes for galactosaemia are occasionally detected on screening of patients with cataract, but observations within known affected families suggest that the risk is at most slight. The Duarte/normal heterozygote representing the commonest of the variant forms carries about 75% of the mean normal activity for galactose-1-phosphate uridylic transferase and is not at particular risk of cataract. Minor maternal deficiency or low-normal activity of this transferase or particularly of galactokinase may also be associated with congenital cataracts in an apparently enzymatically normal child, though undefined influences during pregnancy. Deficiencies of other enzymes such as UDP galactose-4-epimerase, which also affect the main hepatic conversion of galactose to glucose phosphates, are not alone associated with cataract, though combination defects as above are not described.

Within the defined genetic disorders the risk of cataract is broadly correlated with the degree of galactose intolerance. Thus homozygotes for galactokinase deficiency or galactosaemia, and double heterozygotes for galactosaemia and low-activity forms of the transferase such as the Rennes variant, show galactose intolerance and cataracts, as is also found with some cases of heterozygous galactokinase deficiency. Heterozygotes for uridylic transferase galactosaemia are not biochemically intolerant. Interestingly, double heterozygotes for galactosaemia and the Duarte variant, with about 25% residual transferase activity, may show mild biochemical galactose intolerance, as do individuals additionally heterozygous for galactokinase deficiency, though cataract or other clinical stigmata may not arise.

Thus an association between galactose intolerance and the risk of cataract is more evident with moderate or severe intolerance. This association is further supported by a study over 3 years of a child with cataracts, trace galactosuria, galactose intolerance, and partial deficiencies of both the above enzymes. She was initially thought to be a double heterozygote for galactokinase and galactose-1-phosphate uridylic transferase deficiency, a combination which has since
been described. Of late, however, intolerance to galactose as determined by an oral test has improved in parallel with a reduction in the degree of deficit for both enzymes, and a family study has confirmed that known monogenic disorders are not involved. The child represents a new and possibly acquired syndrome, and the further implications of galactose intolerance in relation to cataract are discussed.

**Case report**

**PRESENTATION AND INITIAL ASSESSMENT**

A girl aged 7½ was referred for assessment of a left intermittent divergent squint: bilateral lamellar cataracts with a nuclear element, left more than right, were then observed (Fig. 1). Routine investigation of juvenile cataract included blood for calcium, protein, and glucose—all normal—and urine for sugars by thin-layer chromatography—galactose identified. Enzyme studies on fresh erythrocytes then followed. They indicated borderline deficiency of galactokinase at 1·0 μM galactose consumed/g Hb/hour (normal>1·0 unit) and clear deficiency of galactose-1-phosphate uridyl transferase activity at 13·6 μM galactose consumed/g Hb/hour (normal>18 units). These deficiencies were confirmed 3 months later with values of 0·9 and 11·6 units, respectively, by an improved method for the transferase. All data cited were derived from consistent triplicate determinations for galactokinase and duplicate or triplicate values for transferase activity.

Galactose tolerance was assessed by a new procedure in which an oral load of 20 g galactose incorporating 200 mg of the nonmetabolised sugar 3-O-Me-glucose is administered in the fasting state (Menzies and Mount, in preparation). Results are expressed as the ratio of galactose to 3-O-Me-glucose present in the urine output over the next 5 hours. Normal adults and juveniles have galactose/3-O-Me-glucose excretion ratios below 6, mean value approximately 2·0. Retarded galactose metabolism (intolerance) increases this ratio, and our patient was clearly intolerant with an excretion ratio of 10·6.

**FURTHER ASSESSMENT**

The child had been born by lower segment caesarian section at 32 weeks owing to cessation of growth. Her weight at birth was 2 lb 6 oz (1077 g). She had incubator support for some weeks and returned home at 2 months. The mother had a definite rubella contact during early pregnancy. The child was rather small, but general physical examination was otherwise normal. Visual acuity was R 6/12, L 3/60. The fundi were not clearly seen, but there was no evidence of retrolental fibroplasia. There were some behavioural and reading difficulties at school, and the child still preferred assistance with dressing.

It was not established that the cataracts and possibly also the behavioural problems arose in consequence of the galactose intolerance. However, a trial of galactose restriction was undertaken as systemic galactose problems were evident, the cataracts were not extensive and were of uncertain duration, and in view of the clear evidence of regression of early galactose-dependent cataracts on dietary control. Good family compliance was reported. After 12 months the opaci-
ties and behavioural problems remained unchanged and the diet was discontinued. Galactose intolerance was confirmed 3 months later, the galactose/3-O-Me-glucose excretion ratio then being 13:8.

**FAMILY STUDIES**

Our patient is the only child of healthy unrelated English parents. The mother showed normal erythrocyte galactokinase activity and borderline transferase deficiency at 17.5 μM galactose consumed/g Hb/h (normal >18). The father showed normal transferase activity with borderline galactokinase activity at 0.9 μM galactose consumed/g Hb/h (normal >1.0). But neither parent was galactose intolerant, showing galactose/3-O-Me-glucose excretion ratios of 2:1 and 1.33 respectively. A maternal half-brother then aged 18 years showed an excretion ratio of 5:8. Analysis by isoelectrofocusing of the galactose-1-phosphate uridyl transferase activity in fresh haemolysates from the parents and subsequently from the patient indicated that the patterns for heterozygous galactosaemia, Duarte, and other defined variant forms of this enzyme were not present.

**PRESENT STATUS**

Further investigations were performed at the age of 9½, 9 months after cessation of the special diet. The erythrocyte galactokinase activity was then 1.8 units—that is, normal—and the transferase activity was 15.5 units, still somewhat below normal. Galactose tolerance had also improved, with an excretion ratio of 7:0. Liver function tests were normal. The cataracts were unchanged. The child had transferred to a school for educationally subnormal children and was making good progress there and at home, possibly showing some real behavioural improvement.

Early ovarian failure may occur in girls with galactosaemia, but this influence was not considered in view of the incomplete nature of the enzyme defects and the absence of major familial effects. The child does not have Fanconi syndrome, which may be associated with galactose intolerance independent of enzyme defects in the galactose to glucose pathway.

**Discussion**

This patient has shown clearly defined galactose intolerance fluctuating in parallel with partial deficiency of galactokinase and galactose-1-phosphate uridyl transferase activity. It may be reasonably assumed that these 2 phenomena are related, although the causation of the enzyme deficiencies is not clear. Erythrocyte galactokinase activity is normally increased during early life, and heterozygotes for galactokinase deficiency then show activity well within the normal range for adults, further complicating assessment in young children. However, the adult range normally applies beyond about age 5 years, and particularly in view of the increase in activity later recorded, and the family data, our patient cannot be regarded as a heterozygote for galactokinase deficiency. The further electrophoretic analysis and family studies also exclude heterozygous galactose-1-phosphate uridyl transferase deficiency and known low-activity variant forms of this enzyme. However, the presence of other genetic influences is indicated by the marginal enzyme deficiencies in the parents and the acceptable but reduced galactose tolerance in the maternal half-brother. Galactose tolerance is related to liver function, but gross abnormalities were excluded at a late stage. It remains possible that these or other now diminished acquired influences were previously involved.

Our patient has cataracts and galactose intolerance with a previously undescribed pattern of enzyme defect. We cannot now be certain that the cataracts seen are an expression of the established restriction in galactose metabolism: the age of onset is uncertain and other possible influences, notably prematurity, were also evident. The association is, however, very persuasive in view of the known general background outlined above. The form of cataract arising in patients with partial disorders of galactose metabolism is not consistent and does not help in the recognition of galactose-dependent lesions.

Considerable practical difficulties arise in the investigation of the uncommon rather than rare partial enzyme deficiencies affecting galactose metabolism. Such investigation is worthwhile, since any further consequences within affected families can be defined, and expression may be controlled by early dietary treatment. Evaluation of galactose tolerance may be helpful both in the definition of those patterns of enzyme deficiency which carry a risk of tissue damage such as cataract, and as a pertinent empirical screen for this general group of disorders.

**References**

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