Inexplicable infantile cataracts and partial maternal galactose disorder

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SUMMARY Previous reports have suggested that partial maternal deficiency of galactose metabolising enzymes, particularly of galactokinase activity, could contribute to the formation of cataracts during developmental life, even in a fetus that is enzymatically normal. We have assayed erythrocyte galactokinase and uridyltransferase activities in 12 families with children suffering early onset cataracts. We did not observe any abnormality of galactose metabolising enzymes in either the mothers or the infants. Furthermore, we have looked for the occurrence of cataracts among children of seven mothers heterozygous for one of these two deficiencies. No children with enzyme activity in the normal or heterozygous range had cataracts.

Two genetically determined disorders involving an enzymatic defect in the main galactose metabolic pathway (Figure) are associated with cataracts. The first is uridyltransferase (EC 2.7.7.12.) deficiency, which has long been known as galactosaemia, the other is galactokinase (EC 2.7.1.6) deficiency. Both are autosomal recessive traits. In contrast to the multiple systems affected in galactosaemia, cataract formation is usually the sole stigma in galactokinase deficiency. Early diagnosis and dietary control of these disorders can prevent cataracts and even achieve regression in some cases. The mechanism of cataract formation involves the reduction of galactose to galactitol within the lens. This polyol cannot diffuse out of the lens: it exerts an osmotic effect leading to disruption of the lens fibres. The prevalence of galactokinase deficiency is not well defined (1/40 000 to 1/100), but it is certainly less than for galactosaemia (1/62 000).1

Presenile cataracts have been described in heterozygous patients with galactokinase deficiency,2,3 but other authors, in a larger number of subjects, found no relation between cataracts and partial deficiency.4,5 Heterozygous subjects with uridyltransferase deficiency seem not to have any risk of cataract, although two of 22 patients with presenile cataracts were reported to have a partial deficiency.2

Previous reports have also suggested that partial maternal deficiency, particularly of galactokinase activity, can contribute to the formation of cataracts in utero, even in a fetus that is enzymatically normal.5,6 In view of this hypothesis we have assayed erythrocyte activities of galactokinase and uridyltransferase in families with children suffering from early onset cataracts and have looked for the

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Figure Main galactose pathway (1, 2, and 3) and alternative route responsible for the formation of galactitol (4).

1. Galactokinase
2. Uridyltransferase
3. UDP glucose-4-epimerase
4. Aldose reductase

NADH=nicotinamide-adenine-dinucleotide phosphatase; NADPH=NADP (reduced form); ATP=adenosine triphosphate; ADP=adenosine diphosphate; UDP=uridine diphosphate.
incidence of cataracts among children of mothers heterozygous for these enzyme deficiencies.

**Material and methods**

**Patients.** Two groups of patients were investigated.

Group 1 comprised 24 children with early onset bilateral cataracts and their 12 mothers. The cataracts were observed at birth or in the first few months of life and could not be explained by any specific aetiological factor.

Group 2 comprised seven mothers and their 16 children. Two of these seven mothers had a partial galactokinase deficiency (case 13 was the aunt of a child with homozygous galactokinase deficiency, case 14 happened to be identified in a control group). Four had a partial transferase deficiency, being mothers of children with galactosaemia. One mother (case 19) was explored because she developed cataract during her pregnancy, and she was found to be heterozygous for the transferase deficiency.

**Table 1 Erythrocyte activities of galactokinase and uridyltransferase in children with cataracts and their mothers**

<table>
<thead>
<tr>
<th>Mothers</th>
<th>Case No</th>
<th>Cataract</th>
<th>Galactokinase (µmol/min/kg Hb)</th>
<th>Uridyltransferase (µmol/min/kg Hb)</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<tr>
<td>1</td>
<td>29</td>
<td></td>
<td>418</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td></td>
<td>417</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21-5</td>
<td></td>
<td>373</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21-9</td>
<td></td>
<td>332</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td></td>
<td>Normal*</td>
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</tr>
<tr>
<td>6</td>
<td>21-2</td>
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<td>415</td>
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<td>7</td>
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<td>518</td>
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<td>9</td>
<td>21-7</td>
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<td>10</td>
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</tr>
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<td>11</td>
<td>26-3</td>
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<td>419</td>
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<tr>
<td>12</td>
<td>19-2</td>
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<td>417</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<td></td>
<td>26-0</td>
<td>422-6</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td>6-2</td>
<td>46-6</td>
</tr>
</tbody>
</table>

Reference values for adults: mean (2 SD) galactokinase (n=87)=38.5 (11.2) µmol/min/kg Hb; mean (2SD) uridyltransferase (n=128)=421 (132) µmol/min/kg Hb.

*Screening method of Beutler and Baluda to test uridyltransferase activity.*

**Table 2 Prevalence of cataracts in children of mothers with a partial galactokinase or uridyltransferase deficiency**

<table>
<thead>
<tr>
<th>Mothers</th>
<th>Case No</th>
<th>Cataract</th>
<th>Galactokinase (µmol/min/kg Hb)</th>
<th>Uridyltransferase (µmol/min/kg Hb)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>385</td>
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<td>ND</td>
<td></td>
<td>2.37*</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>ND</td>
<td>3.50*</td>
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<td></td>
</tr>
<tr>
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<td>ND</td>
<td>218</td>
<td></td>
<td></td>
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<td>18</td>
<td>33-4</td>
<td>202</td>
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<tr>
<td>19</td>
<td>22-7</td>
<td>242</td>
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<td></td>
</tr>
</tbody>
</table>

Reference values for adults: mean (2SD) galactokinase (n=87)=36.5 (11.2) µmol/min/kg Hb; mean (2SD) uridyltransferase (n=128)=421 (132) µmol/min/kg Hb.

*Values expressed by ml of packed erythrocytes (hypochromic anaemia).
Methods. Erythrocyte galactokinase and uridyltransferase activities were assayed by isotopic methods using \( (1^{-14}C) \) galactose and \( (u^{-14}C) \) galactose-1-phosphate, respectively, as substrates.\(^7\)

Control values (mean \( (2 \ SD) \)) for galactokinase activity in adults and children above 2 years of age were \( 28.5 \ (11.2) \mu \text{mol/min/kg haemoglobin} \) \( (n=87) \). Galactokinase activity of the infant is three times higher: it decreased during the first year of life; at one year its level is about 1.5 times the adult value.\(^8\)

Control values (mean \( (2 \ SD) \)) for uridyltransferase activity were \( 421 \ (132) \mu \text{mol/min/kg haemoglobin} \) \( (n=128) \) for infants, children, and adults.

Haematological counts were performed to detect patients with microcytic anaemia or a high reticulocyte count.

**Results**

The results are presented in Tables 1 and 2.

**Group 1.** In the families whose children had cataracts (families 1–12) we did not observe significantly reduced galactokinase or uridyltransferase activities in either the mothers or the offspring. The mean values of these enzymes in the mothers were not significantly different from the control means.

**Group 2.** In the families with mothers having partial galactokinase deficiency (families 13 and 14) or partial uridyltransferase deficiency (families 15–19) no cataracts were found in the children in the absence of an homozygote defect. In some healthy children enzymatic activities were not assayed.

**Discussion**

We have explored two groups of patients.

The first group presented ‘inexplicable’ and early onset cataracts in children with normal galactokinase and uridyltransferase activities. We did not find any abnormalities of galactose metabolism in their mothers.

The second group had a partial galactose metabolism deficiency in the mother. No children of these women had cataracts (except the galactosaemic homozygotes). All the pregnancies were allowed to proceed without any restriction of the diet. Nothing is known of the actual milk intake of these mothers during their pregnancy.

These results are disappointing compared with previously reported findings, which hypothesised that a partial enzymatic deficiency in the mother might be responsible for the inexplicable cataracts in some children.\(^5\)\(^6\)

Harley et al have measured galactokinase and uridyltransferase activities in erythrocytes from children with unexplained cataracts, their parents, and matched controls.\(^5\) The mean galactokinase activity in the mothers was significantly lower than that of women controls. No such difference could be shown between the children with cataracts or their fathers and the control group. In our experience the mean galactokinase activity in the mothers with children who had cataracts was not significantly different from the control mean.

Winder et al have reported partial maternal deficiency of galactokinase and transferase activities in 10 families with early onset cataracts.\(^6\) In three families a low lactose diet was prescribed during subsequent pregnancies: two unaffected children were born, but a child with cataracts arose from the third pregnancy. In contrast, our results show that our seven heterozygote mothers had normal children despite the absence of any dietary restriction.

Although plasma lactose concentration (and urinary lactose excretion) increase from the 18th week of pregnancy,\(^11\) it is doubtful whether an appreciable proportion of the circulating lactose is converted into circulating glucose and galactose. Intravenous administration of lactose has been reported not to raise blood glucose concentrations in humans and rats.\(^12\) During pregnancy excretion of galactose is not above normal even in women with a reduced galactose metabolism.\(^13\)

The galactokinase activity in the fetal liver is greater than in the adult organ and is reported to be more responsive to plasma galactose concentration.\(^14\)\(^15\) This may well offer a measure of protection to the fetal lens.

The development of cataracts in the fetus is likely to be the final common pathway of a variety of biochemical insults. Previous studies in the rat noted histological evidence of damage to the fetal lens when pregnant women ingested a diet unusually rich in galactose (40%).\(^16\) In human beings cataract formation in the fetus of an heterozygous mother probably depends on several factors, such as large milk intake, maternal hepatic dysfunction, or mild biochemical ‘intolerance’. After an intravenous loading test with 0.35 g/kg body weight, the half life of galactose and excretion of galactitol are significantly increased in some individuals heterozygous for galactokinase deficiency.\(^17\)\(^18\)

Protective mechanisms, however, seem to exist in the fetus. The history of family 19 argues for a specific fetal protection. An heterozygous woman for uridyltransferase deficiency developed cataract during the third trimester of her first pregnancy, and again during her second pregnancy. The two children born of these two pregnancies had normal lenses, the first one was heterozygous for uridyl-
transferase activity, the second had normal enzymatic activities. A similar observation has been previously described.19

In contrast to other studies, our results do not suggest any direct link between maternal partial galactose disorders and infantile cataracts. More data are needed, however, before previous findings can be ascribed to fortuitous associations.

References


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