Short Reports

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Galactokinase Deficiency in a Newborn Infant

Galactosaemia due to an inborn deficiency of the activity of galactose-l-phosphate uridylyltransferase has been well recognized to result in severe damage to eyes, liver, kidneys, and brain. Deficiency of the preceding galactokinase activity, so that galactose is not converted to galactose-l-phosphate, was first described in a 43-year-old man in 1965 (Gitzelmann, 1965), though the 'galactose diabetes' had previously been reported in the same patient in 1933 (Fanconi, 1933). Subsequently 2 of 3 similarly affected sibs in this Swiss gypsy family were studied (Gitzelmann, 1967), and it appeared that the only clinical manifestation of this enzyme defect was bilateral recurring cataracts. In 1968 galactokinase deficiency was seen in a newborn infant after the detection of a high blood galactose level during a routine screening programme by the metabolite inhibition technique of Guthrie (Thalhammer, Gitzelmann, and Pantlitschko, 1968). This infant showed none of the severe disturbances associated with galactosaemia, though mild hepatosplenomegaly was observed, but the early start of treatment with a galactose-restricted diet made it uncertain whether cataracts would have later developed. Another case of galactokinase deficiency in a neonate also detected through a routine screening programme was reported in 1970 (Dahlqvist, Gamstorp, and Madsen, 1970). Lens opacities were present by the age of 5 weeks, and had almost cleared on a galactose-free diet by the age of 5 months. There was no hepatomegaly or jaundice. This infant's parents, one brother, and possibly one sister were considered to be carriers of an autosomal recessive gene as the enzyme activity of their erythrocytes, determined by a quantitative technique, was roughly half the normal value.

We describe here another example of galactokinase deficiency exhibiting the early development of bilateral cataracts diagnosed during the neonatal period.

Case Report

A female infant of unrelated Pakistani parents was born after 34 weeks' gestation on 29 December 1970. Birthweight was 1·95 kg; length 42 cm; head circumference 28·5 cm. Apgar score was 10 at 2 min. Phenobarbitone 8 mg intramuscularly twice daily was started on the first day of life and continued for 7 days (as part of a random control trial already in progress). Jaundice was noted after 48 hours, and at the age of 4 days, on 2 January 1971, the serum indirect bilirubin level reached a maximum of 22·8 mg/100 ml. No neurological disturbances were noted, and by 21 days of age, 19 January 1971, the serum bilirubin had fallen to 1·1 mg/100 ml. The liver was palpable 1⅓ finger breadths below the costal margin but did not feel abnormal in consistency. Feeds of Ostermilk No. 1 were started at 24 hours of age after earlier feeds of glucose/water. On 2 January 1971 routine urine testing revealed a positive Clinistest but negative reaction to Clinistix. The total blood sugar was 87 mg/100 ml; true blood glucose was 45 mg/100 ml. A 'Galacto-Screen' test for galactose-l-phosphate uridylyltransferase activity gave a normal result. On 8 January 1971 a quantitative measure of this enzyme activity was 8·1 units per g Hb (low normal). A large discrepancy between total blood sugar and true blood glucose levels was frequently recorded (Table).

<table>
<thead>
<tr>
<th>Date</th>
<th>Total Blood Sugar (mg/100 ml)</th>
<th>True Blood Glucose (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2·1·1971</td>
<td>87</td>
<td>45</td>
</tr>
<tr>
<td>8·1·1971</td>
<td>133</td>
<td>55</td>
</tr>
<tr>
<td>11·1·1971</td>
<td>102</td>
<td>43</td>
</tr>
<tr>
<td>14·1·1971</td>
<td>221</td>
<td>38 (3 hr after feed)</td>
</tr>
<tr>
<td>14·1·1971</td>
<td>286</td>
<td>104 (1 hr after feed)</td>
</tr>
<tr>
<td>19·1·1971</td>
<td>208</td>
<td>66</td>
</tr>
<tr>
<td>2·2·1971</td>
<td>108</td>
<td>51</td>
</tr>
</tbody>
</table>

Urine chromatography on 5 and 8 January 1971 showed normal amino acid patterns, and the reducing substance was established as galactose. The routine Guthrie screening test on 12 January 1971 showed a blood galactose level in excess of 100 mg/100 ml (blood taken 1½ hours after a feed). A similar finding was confirmed when the test was repeated.
**Galactokinase activity.** This was tested on the 45th day of life, 12 February 1971 by a modification of the technique described by Ng, Donnell, and Bergren (1965), which obviated the necessity of using radioisotopic galactose. Using larger volumes of 50% haemolysate (2 ml), galactose, ATP, and buffer in the proportions detailed by Ng et al., incubation at 37°C was performed for 60 minutes. Control blood specimens were assayed in parallel with the patient’s sample and the final supernatant solutions were analysed for galactose and galactose-l-phosphate. Disappearance of galactose was observed only with the controls. To prove that the galactose had been converted to galactose-l-phosphate the supernatant solutions following the period of incubation were employed as substrate in a standard procedure (Sigma Technical Bulletin No. 600-UV) designed to measure galactose-l-phosphate uridylyltransferase activity. Erythrocytes from the present patient had, of course, already been shown to have normal galactose-l-phosphate uridylyltransferase activity using the same procedure in its standard form. Confirmation was achieved that blood from the patient produced no detectable galactose-l-phosphate, while that from the controls had formed enough galactose-l-phosphate to replace the galactose-l-phosphate normally used in the assay. It was thus shown that erythrocytes from the control bloods converted galactose to galactose-l-phosphate while those from the patient failed to do so.

**Ocular examinations.** These started with the first detailed assessment on 14 January 1971 at the age of 16 days. This showed no evidence of cataract and normal ocular fundi; there was a small hyaloid remnant at the posterior pole of the right lens. On 25 January 1971 at the age of 27 days, early nuclear cataracts were present in both eyes. The lens opacities were confined to the nuclear region and had the ‘oil globule’ appearance which is seen in classical galactosaemia. Examination under anaesthesia on 11 February 1971 showed also the presence of fine opacities along the posterior lens sutures lines. The cataracts now caused an adventitious myopia which rendered the view of the fundus very distorted.

**Effects of treatment.** From 24 February 1971, when the infant was 57 days old, she was fed on Cow and Gate Low-Lactose Milk, Ketovite tablets, and liquid and mineral supplements (Francis and Dixon, 1970). On that date her weight was 3·57 kg, and her head circumference 34·5 cm. On 8 March 1971 an iron supplement in the form of ‘Sytrin’, 5 ml daily, was started as the Hb was 9·6 g/100 ml. By 11 March 1971 ocular examination showed conspicuous regression of the lens opacities, and by 18 March 1971 the lenses were virtually clear. On the latter date it was decided to test the persistance of galactokinase deficiency by giving four-hourly feeds of Ostermilk No. 1, 180 ml for 24 hours. The results were as follows: Total blood sugar 1 hr after low-lactose feed, 122 mg/100 ml; true blood glucose 1 hr after low-lactose feed, 112 mg/100 ml; total blood sugar 1 hr after Ostermilk feed, 300 mg/100 ml; and true blood glucose 1 hr after Ostermilk feed, 84 mg/100 ml. During the period of Ostermilk feeding the urine again gave negative Clinitest and positive Clinitest results at the 2% level.

The infant was discharged from hospital, weight 4·31 kg on 22 March 1971 to return to Pakistan on the dietary treatment outlined above. Psychomotor development seemed to be within normal limits for the infant’s conceptual age.

**Discussion**

The present case confirms the experience of the other workers quoted above that an inborn galactokinase defect is not associated with the severe and widespread tissue damage which occurs in galactose-l-phosphate uridylyltransferase deficiency. The principal and probably the only consequence of galactokinase deficiency seems to be cataract formation. The obvious nonobstructive jaundice which developed in our patient was probably related only to the premature birth and it had disappeared before a galactose-restricted diet was started. The cause of the cataract is likely to be the formation of galactitol in the lens (and other tissues). The formation of this sugar alcohol from galactose is catalysed by aldose reductase which does not require previous phosphorylation of the substrate (van Heyningen, 1959). The mild hepatosplenomegaly noted by Thalhammer et al. (1968), and the possible transient hepatomegaly in our patient are likely to have little significance. They might be the result of tissue swelling due to osmotic effects of galactitol accumulation. In one of the adult patients of the Swiss gypsy family, investigation revealed an unsuspected latent diabetes mellitus, but it is not known whether this is to be regarded as a late result of galactokinase deficiency (Gitzelmann and Illig, 1969). The important fact to record from our patient is that early cataracts from this enzyme deficiency resolved completely on a low-lactose diet. The increasing use of neonatal screening programmes is likely to uncover more cases of galactokinase deficiency, though it has been pointed out that hypergalactosaemia may be missed if the blood sample is collected just before the first feed of the day, or too long after a feed (Thalhammer et al., 1968). Early treatment is obviously completely successful in preventing or curing cataract formation. Finally, the report of a transient galactokinase deficiency in a newborn infant (Vigneron et al., 1970) seems to make it advisable to test the affected infant with a galactose load from time to time.
Summary

A case of galactokinase deficiency is described in a newborn infant of Pakistani parents. Bilateral cataracts developed by the age of 27 days and completely disappeared on treatment with a galactose-restricted diet. There was no evidence of disturbance of function in other tissues.

REFERENCES


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Trial of Amino Acid Supplements in Cystic Fibrosis of the Pancreas

In cystic fibrosis (CF) patients with malabsorption, bacterial degradation of unabsorbed dietary protein leads to abnormally high urinary excretion of aromatic acids, phenylacetylglutamine and p-hydroxyphenylacetic acid, derived from phenylalanine and tyrosine, respectively (Seakins, Ersser, and Gibbons, 1970). The complete replacement of dietary protein by an amino acid mixture in CF resulted in a fall in urinary phenolic acid excretion (Gibbons, Ersser, and Seakins, 1969) and an improvement in the faecal amino acid pattern (Seakins et al., 1970). It was thought that this biochemical change towards normality might give some clinical advantage due to improved absorption of amino acids, particularly as it had been suggested that p-hydroxyphenylacetic acid might play a part in the susceptibility of patients with CF towards staphylococcal bronchial infections (May, 1969).

This note reports a trial on three patients with CF who had severe symptoms of malabsorption with abdominal distension and discomfort, and who passed bulky and offensive motions.

Clinical and Laboratory data

The 3 children chosen were girls with a proven diagnosis of CF, aged at the beginning of the trial, 3 years 4 months (Case 1), 3 years 11 months (Case 2), and 7 years 7 months (Case 3). Tryptic activity in stools or duodenal juice was abnormally low in all 3 (Case 1, stool tryptic activity, 4 units, normal 10–80; Case 2, duodenal juice tryptic activity less than 1 unit; and Case 3, 7 units, normal 10–60 units). The children received a low fat diet and pancreatin supplements, and the eldest child (Case 3) had been previously given a trial of medium chain triglycerides without lasting improvement. None of the children was grossly undergrown, though the youngest (Case 1) had fallen from the 25th to the 10th centile for both weight and height over the previous 15 months, and the weight centile of Case 2 had also fallen (from 40th to 10th) over the previous 2 years. Respiratory symptoms had been mild, though all had grown coagulase-positive staphylococci in throat swabs at some stage of their disease. Immediately before the trial period, however, repeated throat swabs had grown only commensals, and chest x-rays had shown minor changes of the disease.

The Table summarizes the parameters that were monitored during the study. From the data provided by the mothers over a period of one month, the average daily intake of calories, protein, carbohydrate, and fat were calculated for each child.

The children were then admitted to hospital and kept

<table>
<thead>
<tr>
<th>Daily</th>
<th>Weekly</th>
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<tbody>
<tr>
<td>Stools</td>
<td>Number per day</td>
</tr>
<tr>
<td>Consistency: formed semiformed fluid</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>Offensiveness: +/−</td>
<td>Abdominal circumference (cm)</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>Abdominal pain +/−</td>
</tr>
</tbody>
</table>

Laboratory studies

Full blood count, bleeding studies, liver function tests, serum protein and electrophoretic strip, serum iron and iron-binding capacity, serum folate, serum calcium, blood urea, serum amino acids, 24-hour urine was collected for amino acids and phenolic acids and a 24-hour stool estimation was sent for amino acid measurement.
Galactokinase deficiency in a newborn infant.

M M Kerr, R W Logan, J S Cant and J H Hutchison

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