Galactosaemia in Three Rhodesian Infants

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SUMMARY

The clinically relevant types of genetic galactosaemia involve deficiency of galactose-1-phosphate uridylytransferase (EC 2.7.7.12) or galactokinase (EC 2.7.1.6). Specific diagnosis is made by quantitative assay of these two enzymes. Seven Black patients were referred from Harare Hospital, Rhodesia, with features suggestive of galactosaemia. Enzyme assay identified classic homozygous transferase deficiency in 3 of these patients. The incidence in this population was calculated to be 1:52 000.


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The term galactosaemia is applied to a variety of inherited metabolic defects affecting galactose metabolism. Two clinically significant types are known, designated transferase deficiency and galactokinase deficiency galactosaemia. These result from absent or markedly reduced uridine diphosphate glucose: a-D-galactose-1-phosphate uridylytransferase (EC 2.7.7.12) and adenosine triphosphate glucose D-galactose-1-phosphotransferase (EC 2.7.1.6) activities respectively. Deficiency of the epimerase enzyme (EC 5.1.3.2) gives rise to an asymptomatic condition.

Transferase deficiency is the more common and serious disorder, and may lead to failure to thrive, cataracts, hepatic damage, mental retardation, and early death. Early diagnosis and appropriate restriction of dietary galactose allow normal development to take place.

We report on the presence of transferase deficiency galactosaemia in 3 Black Rhodesian infants.

METHODS

Blood was collected into tubes containing heparin 20 U/ml from 7 children with clinically suspect galactosaemia. The samples were air-freighted to the Red Cross War Memorial...
Children's Hospital, Cape Town, in a sealed plastic bag, containing ice, enclosed in a polystyrene container. Age- and weight-matched controls were included. The average time between sampling and arrival was 24 hours; no specimen took longer than 48 hours.

The transferase activity was assayed in whole blood by a fluorometric technique and galactokinase activity was determined by a radiometric assay. All other analyses were performed according to standard laboratory methods.

**CASE REPORTS**

**Case 1**

This patient, weighing 3 kg, was admitted at the age of 6 weeks in April 1976 with failure to thrive. He had been born at full term by normal vaginal delivery. Cataracts and hepatosplenomegaly were not present. The patient was readmitted at the age of 3½ months with continued failure to thrive and on this occasion hepatosplenomegaly was present. Again cataracts were not detected, but the reducing substance present in the urine was identified as galactose by chromatography. The infant, who was still being breast-fed, was discharged but was readmitted at the age of 7½ months with persistent hepatosplenomegaly. Blood was sent for specific enzyme assay, but pending definitive diagnosis the patient was placed on a milk-free diet. An immediate clinical improvement was observed — the child started to sit, smile and to gain weight. He was readmitted at 11 months of age with bronchitis but had continued to gain weight (5.5 kg) and was sitting up and handling objects.

**Case 2**

This female infant was admitted at the age of 8 months in July 1976 weighing 4.7 kg. The mother had observed retarded mental and physical development for the previous 4 months, and more recently jaundice, cataracts, and oedema of the legs had developed. On examination, the patient's liver was hard and enlarged to 7 cm below the costal margin. Bilateral cataracts and ascites were present, muscle tone was reduced, there was no head control, and the child cried constantly. Galactose was identified in the urine by chromatography, and blood was sent for enzymatic analysis. Despite a milk-free diet the condition of the patient deteriorated rapidly and she died a month after admission.

Almost 1 year later the child's brother was admitted at the age of 1 month with jaundice, lethargy and vomiting. Cataracts and hepatosplenomegaly were present. Galactose was demonstrated in the urine by chromatography. In view of the family history, and confirmation of the diagnosis in the patient's sister (case 2) by enzyme assay, he was put on a lactose-free diet. Since his discharge, he has not been seen again.

**Case 3**

A female infant was admitted at the age of 5 months in August 1976 with a history of jaundice for 1 month and failure to gain weight. She had been born by normal
vaginal delivery, weighed 3 kg at birth, and the early neonatal period had been uneventful. On examination, she was small and wasted, weighing 3.4 kg. She was anaemic, and hepatosplenomegaly and bilateral cataracts were present. Blood was sent for specific enzyme assay, and the child was placed on a milk-free diet. One month later significant weight gain was noted, but the patient has not been followed up since.

RESULTS
In 3 of the 7 suspected cases, the diagnosis of transferase-deficiency galactosaemia was confirmed. Clinical details of these cases and the biochemical data can be seen in Table I.

DISCUSSION
Besides the classic transferase deficiency, a number of electrophoretically distinguishable variants of the transferase have been described, including Duarte, Los Angeles, Rennes, Indiana, Chicago and Berne (Table II). In all instances, enzyme activity is abnormal, generally reduced, and the homozygous state may indicate clinically significant disease.

Mixed heterozygote forms may also result in markedly reduced transferase activity. It is therefore pertinent to enquire into which category the 3 transferase-deficient patients should be placed.

The transferase activity of the 3 subjects with galactosaemia was 6% (case 3), 12% (case 1) and 21% (case 2) of the mean value of our controls. These levels are compatible with those described in the Rennes variant and, in the case of patient 2, with the homozygote Chicago variant or a double heterozygote for classic galactosaemia and the Duarte variant. Although it cannot be unequivocally established on the basis of the present evidence, the diagnosis of classic galactosaemia is most likely for the following reasons:

1. The Rennes and Chicago variants are extremely rare and have only been described in a few cases in localized areas.6,7

2. All patients presented with marked failure to thrive and a variety of other severe clinical disturbances, including cataracts, marked hepatic dysfunction (cases 2 and 3), and neurological retardation and vomiting (case 1). A double heterozygote for classic galactosaemia and the Duarte variant has 25% of normal enzyme activity, but is, however, asymptomatic.8

3. The assay method used in this study for the determination of the transferase activity may give a positive reading even in the absence of transferase enzyme activity. A possible basis for this observation has been recently described,9,10 and possibly accounts for the residual activity present in our patients. A more specific radio-isotope procedure has been reported,11 but is not used in this laboratory since our objective was to demonstrate the absence or presence of adequate transferase activity for clinical purposes. For this reason we did not perform starch gel electrophoresis to distinguish unequivocally between classic galactosaemia and the extremely rare variants mentioned above.

To our knowledge, transferase-deficient galactosaemia substantiated by quantitative enzyme assay has not been reported in an indigenous Black population. The article by Bernstein12 should, however, be mentioned here. The condition has been well documented in Black Americans.13,14

Estimated homozygote frequency of the classic form in various population groups has ranged from 1 : 24 500 to 1 : 200 000, the highest incidence reported to date being in a Black American population group (Table III). Reliable estimates of gene frequency are difficult to achieve, for reasons which have been frequently reviewed.

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<thead>
<tr>
<th>TABLE II. VARIANTS OF TRANSFERASE ENZYME</th>
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<td>Variant</td>
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<td>Normal (wild type)</td>
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<td>Symptomatic variants</td>
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<td>Classic</td>
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<td>Rennes6</td>
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<td>Indiana6</td>
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<td>Chicago (mild)</td>
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<td>Asymptomatic variants</td>
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<td>Duarte6</td>
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<td>Los Angeles7</td>
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<td>Berne38</td>
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All procedures were carried out with whole blood or isolated red blood cells.
The rarity of the condition, also occur, if milk forms a major portion of the diet. In African countries, where breast feeding is imperative for survival, we feel that every effort should be made to confirm a clinical diagnosis of galactosaemia before the child is put on a lactose-free diet.

When a specimen of blood is sent to a distant laboratory for enzyme assay, it must be sent on ice together with age- and weight-matched controls. The transit time should be less than 48 hours and if it is possible, prior notification of the referral laboratory will avoid undue delay in analysis. A full clinical and biochemical documentation should accompany each specimen.

**REFERENCES**