Hereditary Galactokinase Deficiency

J. G. H. COOK, N. A. DON, and TREVOR P. MANN

From the Royal Alexandra Hospital for Sick Children, Brighton, Sussex

Cook, J. G. H., Don, N. A., and Mann, T. P. (1971). *Archives of Disease in Childhood*, 46, 465. **Hereditary galactokinase deficiency.** A baby with galactokinase deficiency, a recessive inborn error of galactose metabolism, is described. The case is exceptional in that there was no evidence of gypsy blood in the family concerned. The investigation of neonatal hyperbilirubinaemia led to the discovery of galactosuria. As noted by others, the paucity of presenting features makes early diagnosis difficult, and detection by biochemical screening seems desirable. Cataract formation, of early onset, appears to be the only severe persisting complication and may be due to the biosynthesis and accumulation of galactitol in the lens. Ophthalmic surgeons need to be aware of this enzyme defect, because with early diagnosis and dietary treatment these lens changes should be reversible.

Galactokinase catalyses the conversion of galactose to galactose-1-phosphate, the first of three steps in the pathway by which galactose is converted to glucose (Fig.).

FIG.—Conversion of galactose to glucose.

ATP = Adenosine triphosphate.

ADP = Adenosine diphosphate.

UDP Glucose = Uridine diphosphoglucose.

UDP Galactose = Uridine diphosphogalactose.

NAD⁺ = Oxidized nicotinamide adenine dinucleotide.

In 1965 Gitzelmann described hereditary galactokinase deficiency in a man aged 42 years with recurrent bilateral cataracts originating in early infancy. At the age of 9 years a diagnosis of neurofibromatosis (von Recklinghausen's disease)

and galactose diabetes had been made in this patient (Fanconi, 1933). In adulthood he was found to have glycosuria as well as galactosuria, and an unexpectedly high level of urinary galactitol was detected. He was of average intelligence, and his handicaps, apart from poor vision, appeared to be due to neurofibromatosis. There were two sisters with long-standing cataracts who were otherwise well and of normal intelligence. The elder, aged 64 years, proved to have the same enzyme defect (Gitzelmann, 1967). She did not show glycosuria, but urinary galactitol was found in spite of a low milk intake, the level being only slightly less than that of urinary galactose. Aminoaciduria was not a feature of the two cases studied. The parents were related members of a Swiss gypsy family, and the mother, like the son, suffered from neurofibromatosis. The inheritance appeared to be that of an autosomal recessive condition.

Subsequently galactokinase deficiency has been recognized in two neonates, one born in Austria (Thalhammer, Gitzelmann, and Pantlitschko, 1968) and the other in Germany (Linneweh, Schaumlöffel, and Vetrella, 1970) and both of gypsy parentage. The first was detected with the help of a screening programme, hypergalactosaemia being found in a specimen taken two hours after a feed on the seventh day. Enzyme studies then demonstrated galactokinase deficiency. The infant thrived and remained well on cow's milk, but hepatosplenomegaly was noted between the second and third weeks of life and circumscribed lens

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opacities were observed as early as 3 weeks. The eye changes regressed and the liver returned to a normal size on a low lactose diet. There was no family history of cataracts, mental retardation, or liver disease. The second affected baby was the result of a consanguineous marriage and though the parents had normal eyes there was a family history of cataracts. A sugar was found in the urine a week after birth which was galactose. After 5 weeks of standard milk feeding lens changes appeared but cleared on a low lactose diet. There were no other pretreatment signs and growth was normal. Neither of these neonates showed amino-aciduria or glycosuria while receiving lactose. In contrast to the usual situation in galactose-1-phosphate uridyl transferase deficiency (congenital galactosaemia) disease manifestations were notably absent.

We now describe a further example of galactokinase deficiency presenting on the 5th day of life with galactosuria, the latter discovered during screening studies for hyperbilirubinaemia. The parents were unrelated and not gypsies. The family history was unrevealing. The paucity of presenting clinical manifestations was again a striking feature.

Case Report

A male infant of 3.9 kg delivered normally at 42 weeks' gestation. Pregnancy normal. He was the third child of healthy unrelated parents with no gypsy blood in the family. Two brothers were alive and well; all 3 children having fair hair and blue eyes. There was no family history of mental retardation, cataracts, or liver disease.

Hyperbilirubinaemia was noted at 5 days (total bilirubin 14.1 mg, unconjugated bilirubin 13.6 mg/100 ml). Reducing substances were found in the urine on the 5th and 7th day by Benedict's test (negative 'Clinistix'), subsequently identified as galactose by thin-layer chromatography. Quantitative estimation by specific enzyme assay for galactose showed urinary levels of 420 mg/100 ml and 130 mg/100 ml, respectively.

Aged 10 days, he was thriving on a standard full-cream dried milk. There was minimal jaundice but the liver was normal in size and the spleen palpable. Blood galactose 40 mg/100 ml. On the following day blood glucose was 42 mg/100 ml and RBC galactose-1-phosphate uridyl transferase level was normal. A low lactose diet had been introduced 4 days previously, but cow's milk feeding was reintroduced on receipt of the normal transferase result.

Aged 8 weeks he was still thriving on cow's milk, and development was normal with no hepatic or splenic enlargement. Blood galactose 44 mg/100 ml; blood glucose 32 mg/100 ml, but without symptoms of hypoglycaemia.

Ophthalmological opinion: 'Both lenses have a slightly opalescent appearance with Y-shaped sutures visible on direct illumination. On ophthalmoscopy there is a faint impression of nuclear sclerosis but no opacities. If this is due to galactose or derivatives it should clear on treatment.' RBC galactokinase activity was found to be low (Table I). Galactose-1-phosphate accumula-

TABLE I
Erythrocyte Galactokinase Activity (μ moles galactose phosphorylated/g Hb/per hr)

Subject	Age (yr)	Galactokinase Activity
Patient	2/12	0.2
Patient	11/12	None detected
Father	35	0.6*
Mother	29	0.4*
Brother	6	0.7*
Brother	3	1.3

Estimate of normal range of erythrocyte galactokinase activity based on a limited series 1-2 μ moles galactose phosphorylated/g Hb per hr.

*Presumed heterozygotes for abnormal gene.

tion test showed no increase of galactose-1-phosphate in the erythrocytes. Galactosuria disappeared on a low lactose diet which was maintained.

Aged 8 and 10 months cow's milk was reintroduced for 4 and 13 days, respectively. Three 24-hour specimens of urine were collected for galactose, glucose, galactitol, and amino acid estimations (Table II). Urinary

TABLE II
Glucose, Galactose, Galactitol, and Galactosamine Levels in 24-hour Urine Specimens Collected at Ages of 8 and 10 months while Receiving Cow's Milk

Time on Cow's Milk	Age (mth)	Urine Volume (ml)	(mg/100 ml urine)			
			Glucose	Galactose	Galactitol	Galactosamine
24-48 hr	8	780	<2.5	530	24	30.14
72-96 hr	8	675	<2.5	450	73	12.17
13 dy	10	618	<2.5	460	136	13.68

Above determinations, together with amino acid assay, by Dr. Richard Gitzelmann, University Paediatric Department, Kinderspital, Zurich.

amino acid assay showed, in all three specimens, a high excretion of a fraction eluting in the position of galactosamine; this was particularly marked in the first specimen collected 24–48 hours after the reintroduction of cow's milk, at the age of 8 months. No clinical side effects and no recurrence of hypoglycaemia followed these periods of lactose ingestion. Blood galactose levels were in the range 10–30 mg/100 ml. Urine was usually negative to 'Clinitest' in specimens collected during the first hour after completion of a feed, but usually positive (values up to 2%) in second and third-hour specimens (Table III).

At 11 months, RBC galactokinase activity was studied in the patient and his immediate family (Table I).

At 18 months he remained a healthy baby of normal development and nutrition with no lens changes. Low lactose diet has been continued with full vitamin supplements.

Methods

Identification of urinary galactose by thin-layer chromatography on Keisegel G (Merck); solvent ethylacetate–ethanol–water (132+60+8); time of run 1 hour; location reagent (spray): 10 ml 85% orthophosphoric acid + 100 ml reagent consisting of 1 ml aniline, 1 g diphenylamine, 100 ml acetone. Galactose = blue spot, after heating at 100 °C for 10 minutes (R_g value 0.81). Blood glucose estimation by Auto Analyser: glucose/peroxidase method.

Quantitative blood and urine galactose by the commercially available Boehringer Biochemica test combination based on oxidation by galactose dehydrogenase. RBC galactose-1-phosphate accumulation by a modification of the method of Schwarz (1960).

RBC galactose-1-phosphate uridyl transferase assayed by a method based on the uridine diphosphoglucose consumption test of Kalckar, Anderson, and Isselbacher (1956).

RBC galactokinase activity assayed according to the method of Ng, Donnell, and Bergren (1965).

Urinary galactitol assayed by gas liquid chromatography as described by Gitzelmann, Curtius, and Müller (1966).

Urinary amino acid estimation by the method of Stein and Moore (1954).

Screening test: 'Clinitest' performed on a sample of urine collected 2 hours after subject has taken 600 ml milk and 150 ml yogurt.

Discussion

Hereditary galactokinase deficiency is a very rare metabolic disorder which apparently produces no dramatic disease manifestations in the early weeks and months of life. Diagnosis at this time is, therefore, difficult even when the clinician is fully aware of the existence of the disturbance. In cases which pass unrecognized, lens changes may progress insidiously and be far advanced by the time failing vision attracts medical attention.

Unexplained hyperbilirubinaemia in the first

week or so of life, should, in future, bring to mind the possibility of galactokinase deficiency, and the differential diagnosis of obscure hepatic and splenic enlargement in the young infant must henceforth include this enzymopathy (Thalhammer *et al.*, 1968). The finding of a blood glucose level of 32 mg/100 ml in our patient at the age of 8 weeks, while he was still receiving cow's milk, suggests that this disorder may lead to hypoglycaemia.

Because similar diagnostic difficulties may at times arise with variant forms of galactose-1-phosphate uridyl transferase deficiency, it seems desirable for these two inborn errors of galactose metabolism, both producing hypergalactosaemia and galactosuria shortly after birth once feeding is established, to be included in detection programmes for hereditary biochemical disorders. As the hypergalactosaemia associated with galactokinase deficiency may be inconstant and virtually absent in the fasting state, the timing of blood collection in relation to feeds is critical. Similar care is necessary when using urine for screening purposes as galactosuria may also be intermittent. Thus, when cow's milk was reintroduced into the diet of our patient for a few days at the age of 8 months and for a longer period 2 months later, we observed that galactose was usually absent from urine collected during the hour after completion of an adequate feed, particularly the first one of the day, but present in significant amounts in the second and third hour specimens (Table III). Accordingly, the recommendation of Thalhammer *et al.* (1968) that, ideally, blood and urine for galactose detection should be collected 1 to 2 hours after a feed, and not the first one of the day, seems sound and our experience suggests that too much reliance should not be placed on a single negative urine test. The finding of hypergalactosaemia or galactosuria does not, of course, indicate the existence of an inborn error of galactose metabolism, because it is well recognized that very occasionally the galactose level in the blood of a normal infant may rise after a feed to about 40 mg/100 ml (Woolf, 1962) and when this happens a spill-over of the sugar into the urine may occur. The finding of galactose in the blood or urine of a neonate should, therefore, prompt one to carry out enzyme tests necessary to establish a firm diagnosis.

Our knowledge of the long-term clinical effects of untreated galactokinase deficiency is at present limited, but seemingly progressive cataract formation is the only major lasting complication. There is growing evidence to suggest that the biosynthesis and accumulation of galactitol, an osmotically active sugar alcohol derived from galactose, is the

TABLE III
Reducing Substances in Urine After Cow's Milk Feeds Reintroduced at Ages of 8 and 10 Months

Time of Completion of Feed	Consecutive Hourly Collections	'Clinitest'
<i>Aged 8 months</i>	1230 hr	1st Neg.
		2nd 0.5%
		3rd —
	1800 hr	1st Neg.
		2nd 0.25%
		3rd 2%
	0700 hr	1st Neg.
		2nd 0.75%
		3rd 1%
	2300 hr	1st 0.75%
		2nd 1%
		3rd —
	0715 hr	1st Neg.
		2nd 0.5%
		3rd 1%
<i>Aged 10 months</i>	1200 hr	1st Neg.
		2nd 0.25%
		3rd Neg.
	1700 hr	1st Neg.
		2nd 2%
		3rd Neg.
	0700 hr	1st Neg.
		2nd 1%
		3rd Neg.
	1200 hr	1st 0.5%
		2nd Neg.
		3rd Neg.
	1900 hr	1st 0.25%
		2nd 0.5%
		3rd 2%

direct cause of the lens changes in galactose-1-phosphate uridyl transferase deficiency (Kinoshita, 1965; Gitzelmann, 1967). The same mechanism is even more likely to be responsible for the cataracts in galactokinase deficiency, since little or no metabolism of galactose takes place by the normal pathway. Galactose build-up then stimulates the activity of the enzyme aldose reductase, present in relatively large amounts in the lens, which with the coenzyme reduced nicotinamide adenine dinucleotide phosphate catalyses the conversion of galactose to galactitol (Sidbury, 1969). Certainly this polyol was found in increasing amounts in the urine of our patient after the reintroduction of lactose feeding (Table II), and substantial amounts were found in the urine of Gitzelmann's presenting case (Gitzelmann, 1967), due presumably, in both instances, to the synthesis of galactitol in the tissues, in general, and the lenses in particular.

Clinicians other than paediatricians, particularly ophthalmologists, need to be aware of this metabolic disorder, so that children and older subjects with unexplained cataracts can be suitably screened (see Methods). The index of suspicion should be

especially high if this lens disturbance is found in an individual of gypsy extraction. As the mechanism of toxicity to the lens at the biochemical level seems to be the same in these two disorders of galactose metabolism, and as established cataracts associated with the transferase defect may sometimes regress with the help of a low lactose diet (Woolf, 1962), it seems likely that the same dietary treatment, especially when coupled with surgery, may lead to restoration of useful sight in some cases of galactokinase deficiency, recognized only late.

For some time now it has been thought that the accumulation of galactose-1-phosphate in the tissues may be responsible for the many and varied disease manifestations in the transferase defect (Kornrower, 1961). A comparison of the clinical features in these two galactose enzyme defects is now becoming possible and supports this view. Thus, in galactokinase deficiency where the phosphate ester is not formed, physical signs are sparse in the early days of life and later clinical effects few. On the other hand in the transferase defect where phosphorylated intermediates are known to accumulate, physical signs are generally plentiful soon after birth, and permanent tissue damage, for instance, to the liver and developing brain, soon becomes evident in the absence of treatment.

Erythrocyte galactokinase activity was assayed in the parents and two sibs of our patient. The values (Table I) support Gitzelmann's view that this enzyme deficiency is transmitted as an autosomal recessive trait. Mayes' estimate of the frequency of galactokinase deficiency, based on the incidence of heterozygotes, was 1 in 40,000 to 1 in 50,000 births (Mayes, 1969). However, a critical scrutiny of his data suggests that he may have overestimated the carrier frequency and an incidence of 1 in 100,000 for this recessive affection would be more realistic, which means that galactokinase deficiency is approximately 5 times less common than the transferase defect. Recently 42 children and young people (14 females and 28 males) aged 3 to 19 years with long-standing cataracts of unknown aetiology have been screened (see Methods) without finding a single example of galactokinase deficiency. A gypsy girl aged 8 years with cataracts of early onset and obscure origin was similarly tested with a negative result. Assuming that the homozygotes would all have developed cataracts in early life, which seems highly probable, it is becoming clear that we are dealing with a very rare inherited metabolic disorder.

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Addendum

Since submitting this paper a further account of hereditary galactokinase deficiency has appeared from Sweden (Dahlqvist, Gamstorp, and Madsen, 1970). Diagnosis was made in the neonatal period as a result of screening using Guthrie's microbial inhibition assay. At the age of 3 weeks the baby seemed physically and developmentally normal. When 5 weeks old, and 10 days after dietary treatment had been started, bilateral cataracts were detected. The parents were unrelated and not gypsies.

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Correspondence to Dr. Trevor P. Mann, Royal Alexandra Hospital for Sick Children, Dyke Road, Brighton BN1 3JN.