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A Duarte Variant with Clinical Signs

Patients with the Duarte variant of galactosaemia are usually healthy, despite functional and structural abnormalities in their galactose-1-phosphate uridylyl transferase (Beutler *et al*, 1965; Mathai and Beutler, 1966; Gitzelman, Poley, and Prader, 1967; Ng *et al*, 1969). We describe an infant with abnormal signs associated with the enzyme phenotype of a homozygous Duarte variant.

Case Report

A 2-month-old boy was admitted to the hospital because of jaundice since the 3rd day of life.

The pregnancy and delivery were normal. He weighed 3.2 kg at birth, was 52 cm long, and had a head circumference of 34 cm. Apgar scores were 9 at 1 minute and 10 at 5 minutes. Physical examination after birth was normal. He was blood group O, type Rh positive, as was his mother. His diet from birth was Enfamil, which he tolerated well. He was slightly jaundiced when discharged from the nursery on the 3rd day; the liver edge was 1 cm below the right costal margin.

He continued to gain, in spite of mild jaundice apparent at office visits at 11 days and 6 weeks of age. The total serum bilirubin concentration at 6 weeks was 3.9 mg/100 ml, of which 3.6 mg/100 ml was in the conjugated (direct reading) form. The jaundice deepened, and the weight gain lessened during the 2 weeks before admission.

He was the 2nd child of healthy, unrelated, 23-year-old parents. His 3-year-old sister had been well as an infant, and there was no history of milk intolerance, jaundice, or liver disease in the family.

He was icteric on admission. The liver was felt 4 cm below the right costal margin; the spleen was not felt. Two veins were prominent in the right upper quadrant. He had signs of a cold. Weight (4.5 kg) and length (55 cm) were in the 25th centile; head circumference (37.5 cm) was in the 10th centile. Motor development was normal.

Total serum bilirubin concentrations on consecutive days were 5.7 and 7.4 mg/100 ml, 3.6 and 3.4 mg/100 ml of which, respectively, were in the conjugated (direct reading) form. The white cell count was 19,650 cells/mm³, with a lymphocytosis of 85%. Red cells values were normal and included a haemoglobin concentration of 12.6 g%, hematocrit of 38.5%, and reticulocyte count of 1.6%. The urinalysis was normal; reducing sugars were not detected. Faecal and urinary urobilinogen, throat and urine cultures, serum protein electrophoresis, and serum enzymes were normal, except for 282 mU/ml of serum glutamic-oxaloacetic transaminase.

A diagnosis of biliary atresia was considered. Other abnormalities found a few days later during evaluation for surgery in another hospital were: a palpable spleen, 1½ cm below the left costal margin; dark, bile-stained urine with excessive urobilinogen; an acholic stool; an elevated, rising aldolase concentration; hematocrit values ranging from 28 to 36% and reticulocytosis of up to 6.2%. The serum bilirubin concentration remained 5.0 mg/100 ml, of which 3.6 mg/100 ml was in the conjugated form. A radioactive rose bengal test suggested but did not confirm an obstruction.

Surgery exposed a green, non-fibrotic liver and an unusually small, bile-containing gallbladder, which was incised, drained, and irrigated. An operative cholangiogram revealed patent ducts and normal flow. The consulting pathologist described 'marked fatty infiltration, bile retention, periportal fibrosis (and cirrhosis) and

pseudoacinar changes' in liver biopsy material and suggested a diagnosis of galactosaemia.

The jaundice faded gradually, and the total bilirubin fell to 1.2 mg/100 ml within 3 weeks. He was then 3 months old, with weight and height in the 25th, and head circumference in the 10th centiles. The liver was 4 cm below the costal margin; the spleen was not enlarged. Motor and mental development were normal.

The infant continued to thrive, except for acute asthmatic bronchitis requiring hospitalization at 4½ months, by which time the jaundice was gone, and the serum bilirubin concentration (0.3 mg/100 ml), haemoglobin (13.8 g) and reticulocyte count (0.5%) were normal. The levels of serum alkaline phosphatase and glutamic-oxaloacetic transaminase, however, were higher than normal.

At 9 months his weight (10.2 kg) and height (72 cm) were in the 75th centile; his head circumference (44 cm), was in the 10th centile. The anterior fontanelle was open. The liver and spleen were not enlarged. Motor development and behaviour were normal. He has been fed whole milk from the age of 5 months.

Methods and Materials

When the patient was 8 months old, we measured the galactose-1-phosphate uridyl transferase in mailed heparinized samples of his blood and that of his parents and sister by fluorescent spot tests (Beutler and Baluda, 1966a) and by fluorometric assays (Beutler and Mitchell, 1968). Transferase activities were again estimated when the boy was 9 months old, this time in fresh samples cooled to 4°C during transit and measured by a uridine-5-diphosphoglucose (UDPG) consumption method (Beutler and Baluda, 1966b). Comparable data from 6 healthy adults, aged 20 to 50 years, and from the literature (Beutler and Baluda, 1966b) served as control values. We separated the isozymes by horizontal electrophoresis of the hemolysates through starch gel for 18 hours at 4°C in a continuous buffer system of Tris, ethylenediamine tetra-acetic acid, sodium chloride, and β-mercaptoethanol (Ng *et al*, 1969), at pH 8.0, and compared them with the normal transferase and with Duarte variant transferase from Dr Ernest Beutler's patients.

Results

Transferase activities in the mailed blood samples were normal, when estimated by the fluorescent spot tests, ie, fluorescence times were similar to those from normal infants (Kelly *et al*, 1970). Measured by fluorometry, however, there was less transferase than expected (Table), especially in the patient. Transferase in the fresh samples, measured by UDPG consumption, also reflected the lower activities: The patient's enzyme levels were approximately half and the parents' and sister's levels, three-fourths those in normal blood.

The isozyme in the patient's hemolysate had the

TABLE
GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE
IN THE PROPOSITUS AND HIS FAMILY

Sample	Galactose-1-phosphate Uridyl Transferase				Isozyme Genotype
	Activity				
	Units/g Haemoglobin		UDPG Consumption	Fluorescence Time (hr)	
	Fluorometry	Test a			
Patient	6.5	7.4	12.6	<3	Gt ^D /Gt ^D
Father		11	17.0	<3	Gt ^D /Gt ⁺
Mother		10	15.0	<3	Gt ^D /Gt ⁺
Sister		10	15.0	<3	Gt ^D /Gt ⁺
Controls	12-15*		18.5-28.5†	<3	Gt ⁺ /Gt ⁺

* Six healthy adults.

† From Beutler and Baluda (1966a and b).

electrophoretic pattern of the Duarte homozygote, ie, a single band which moved faster than normal transferase. The isozymes in the parents' and sister's haemolysates were characteristic of those in the Duarte variant carrier, ie, 2 bands with mobilities of normal and Duarte variant transferases, respectively.

Discussion

Our patient's history suggests that even 'harmless' variants of galactose-1-phosphate uridyl transferase may be symptomatic. Thus, variable expressivity may be a property of the mutant gene for the Duarte variant transferase, as for classical galactosaemia. While the transferase defect may not be the primary or only cause of the jaundice (and, indeed, its recession during recovery from surgery is puzzling), the report of characteristic liver pathology complements the abnormal biochemistry. Conversely, the two recent reports of affected infants with other structural variants of the transferase attest the biochemical variability of the disease (Shapiro and Kaplan, 1969; Chacko, Christian, and Nadler, 1971).

Excluding the possibility of enzyme mosaicism, where the transferase of liver may differ from that of red cells, a likely explanation for the transient clinical signs in our patient is a delayed maturation of the Duarte variant transferase, as may happen occasionally in the infant heterozygote of classical galactosaemia (Kelly *et al*, 1970).

Summary

Galactose-1-phosphate uridyl transferase with the activity and electrophoretic pattern of the Duarte variant homozygote was found in an 8-month-old

boy who had jaundice and liver enlargement during the first 2 months. The parents and sister were carriers of the Duarte trait.

We are very grateful to Dr James W. Sayre, Dr Thomas C. Putnam, and Dr John M. Craig for their medical, surgical, and pathological records, respectively.

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