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Learning from errors

Problems with the new born screen for galactosaemia

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Summary

The new born screen should identify asymptomatic children with a devastating disorder before the damage has occurred. One family had two children born with classical galactosaemia. The first child, subject to a flaw in the newborn screening program, was not detected, went into rapid liver failure and ultimately had a liver transplant. The second child was following the same devastating course when identified by the new born screen with reduced galactose-1-phosphate uridyl transferase activity in a blood spot. The rapid response of the second child to removal of lactose and galactose from the diet resulted in significant clinical improvement. If the screening test for an inborn genetic defect involves the measurement of enzyme activity in red blood cells, be sure the patient has only native red blood cells. The events leading to the failure of the galactosaemia screening test are reviewed, so physicians will be aware and avoid this problem.

BACKGROUND

The newborn screen is a practice of testing every newborn for harmful or fatal genetic disorders before they are clinically manifest. Early intervention for these problems prevents morbidity and mortality. Classical galactosaemia[1] is a genetically determined deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) activity. This deficiency causes accumulation of galactose, galactose-1-phosphate and galactitol in tissues of affected individuals.[1] The primary source of galactose is lactose, found in mammalian milk. Newborn infants are immediately exposed to lactose in human milk and most infant formulas. The clinical signs of this defect (feeding problems, hepatomegaly, jaundice, failure to thrive, cataracts, hypoglycaemia, gram negative sepsis and acute liver failure)[1] become evident during the neonatal period. Liver failure and gram negative sepsis have resulted in death.[2] A common screening method for galactosaemia is the Beutler fluorometric assay[3] which measures GALT activity in blood spots collected on filter paper. Reduced florescence indicates reduced or absent GALT activity. This may identify a genetic defect or deterioration of enzyme activity before analysis. Thus, the screening test only identifies subjects at risk. Diagnostic tests are essential for the correct diagnosis. We report one family's experience with the newborn screen and a problem paediatricians should understand and avoid.

CASE PRESENTATION

Patient A was a 3240 g vigorous female born by spontaneous vaginal delivery at 39 weeks gestation. Initial feedings were breast milk and the new born screening blood was collected at 34 h of age. On day 5, a liver function test was performed because a sibling (patient B) had been diagnosed with liver failure attributed to neonatal haemochromatosis. Patient A had evidence of early liver disease (table 1). It was assumed to be neonatal haemochromatosis and she was transferred to the hospital where patient B had a liver transplant 4 years earlier at 9 weeks of age. Prior to physicians seeing the newborn screen report, patient A had intravenous immunoglobulin and two exchange transfusions administered for neonatal haemochromatosis. Simultaneously, the diet was changed to pregestimil, a cow milk formula with lactose removed. This initial treatment completely corrected her liver function tests and she was taken off the transplant list. The infant screen reported reduced GALT activity < 2.1 U/g Hgb but reliable confirmatory testing could not be performed because of the exchange transfusions. Since liver function improved in response to exclusion of lactose from the diet, further evaluation for galactosaemia by measuring urinary galactitol[4] was not pursued. At 6 months of age, red cell GALT activity was undetected; sequence analysis of the GALT gene showed two mutations, Q188R/Y209C, consistent with classical galactosaemia.

Patient B had a clinical course with certain similarities. She was born at 37 weeks gestation weighing 3107 g. She was breast fed and her newborn screen at 48 h showed a GALT activity of 1.9 U/g Hgb, but the screening laboratory indicated the sample was inadequate and requested a second sample. Before that request was received the child was hospitalised because of poor breast milk feeding and abdominal distension. The hospital course deteriorated with prothrombin time and partial thromboplastin time increasing and total albumin falling to 2.1 g/dl. Her haemoglobin dropped below 7 g/dl (haematocrit 22%) and she

Table 1 Patient A liver function

Day 5
Total bilirubin – 21.9 mg/dl (0.2–1.2 mg/dl)
SGOT – 147 U/l (5–34 U/l)
SGPT – 106 U/l (0–55 U/l)
Alkaline phosphatase 1385 U/l (40–150 U/l)
Day 11
Albumin – 2.7 g/dl (2.9–5.5 g/dl)
PT – 26.5 s (10–12.6 s)
PTT – >124 s (23–39 s)

PT, prothrombin time; PTT, partial thromboplastin time; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

received a transfusion with packed red blood cells. The re-screen for galactosaemia was collected and sent after the blood transfusion and the report indicated normal GALT activity. Patient B continued to show progressive liver failure and was made NPO (receiving only intravenous fluids) for 12 h before a liver biopsy. Following the biopsy the child was started on a soy formula. One day later the biopsy report indicated severe cirrhosis with increased iron within macrophages. The most likely aetiologies suggested were: galactosaemia, tyrosinaemia and hereditary fructose intolerance. Urine was then collected for reducing sugar measurement which was negative. Patient B was then transported to another hospital for a liver transplant. The receiving physicians believed that this child had neonatal haemochromatosis. Because of her emaciated appearance, distended abdomen and ascites her enteral feedings were switched to medium-chain triglycerides rich pregestimil. Her appetite started to improve and vomiting decreased. It was also noted at that time that the child had reduced consciousness, seizures and elevated ammonia so lactulose and neomycin were added to her treatment to lower the ammonia. Lactulose is an oral agent containing 15% galactose used to remove excess ammonia through the intestines. The liver failure continued to progress and a living donor liver transplantation occurred at 9 weeks of age. Patient B recovered from her liver transplantation and was maintained on immunosuppressive medications and enfamil lipil 24 calories/ounce, a lactose containing formula. She was characterised by her mother as a 'picky eater' and had numerous episodes of vomiting and diarrhoea that were attributed to milk protein allergy. Cow milk was removed from her diet.

After patient A was diagnosed with classical galactosaemia, patient B (4 years old) had her red cell GALT activity measured for the first time since her transplant. This revealed absent GALT activity. Sequencing of her GALT gene revealed the same two mutations, Q188R/Y209C, found in her younger sibling.

Both children were placed on a low lactose/galactose diet. During a routine follow-up visit a 3-day diet history indicated the older child (5 and 9/12 years) consumed larger portions of the same foods as the younger sibling (1 and 6/12 years); both children consumed approximately 100 calories/kg/day. At that visit, red cell galactose-1-phosphate and urine galactitol in a first morning specimen were measured (table 2). Despite her liver transplant, patient B had an elevated galactose -1- phosphate in her red blood cells, but a lower urinary galactitol than her sibling. The liver transplant has improved galactose metabolism, but has not corrected the galactosaemia, as manifest clinically by recurring episodes of vomiting and diarrhoea in association with dietary lactose.

DISCUSSION

The initial screening test results for each of these children suggested a defect in GALT activity. In patient A, the confirmatory test was performed after two exchange transfusions; the results indicated normal GALT activity. The progressive liver failure in patient A responded to a lactose-free diet making the clinical diagnosis of galactosaemia likely. Six months after the exchange transfusions, the absence of GALT in her blood was confirmed. In patient B, the confirmatory test occurred after the child had one packed red cell transfusion; results indicated normal GALT activity. A test for reducing sugar in the urine provided another false negative result since it was collected more than 48 h after galactose exposure ended. The next confirmatory test, 4 years later, indicated no GALT activity.

Table 2 Galactose metabolism in two children with the same GALT defect but two genetically different livers

Patient	Weight(kg)	RBC gal-1-P (μg/g Hgb)	Urine galactitol (μM/mM creatinine)
A	9.73	74 (80–125)	254.6 (194–620)
B	18.9	94 (80–125)	126.7 (194–620)

The reference ranges indicated are for individuals with classical galactosaemia on a lactose-free diet. Normal red cell gal-1-P levels range from 5 to 49 μg/gm Hbg and normal urine galactitol is <45.4 μM/mM creatinine.[4]
RBC, red blood cell.

Patient A is an example of new born screening having a major positive impact upon the life of a child. Concomitantly, patient B exemplifies a pitfall of the newborn screen. Paediatricians must be aware that inappropriate interpretation of results from the new born screen can compromise the test's effectiveness. Galactosaemia is an important congenital defect that should be identified by the newborn screen and should always be considered in cases of neonatal liver failure. This defect is identified by reduced enzyme activity in the patient's red blood cells. Neither screening nor confirmatory testing is valid after a transfusion. If galactosaemia is a consideration, it is prudent to introduce low lactose/galactose soy milk[5] to the diet until the diagnosis can be confirmed later with the child's native red blood cells.

Learning points

- Newborn screening tests may prevent the morbidity and mortality associated with inborn errors of metabolism.
- Physicians must understand the screening test results for this approach to be effective.
- A newborn with progressive liver disease must avoid galactose until another aetiology is proven.

Competing interests None.

Patient consent Obtained.

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