Learning from errors
Problems with the new born screen for galactosaemia

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Summary
The newborn 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 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. 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) become evident during the neonatal period. Liver failure and gram negative sepsis have resulted in death. A common screening method for galactosaemia is the Beutler fluorometric assay 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 chronic 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 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...
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 fail-
ure and was made NPO (receiving only intravenous flu-
ids) 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 sug-
gested were: galactosaemia, tyrosinaemia and hereditary 
fructose intolerance. Urine was then collected for reduc-
ing sugar measurement which was negative. Patient B 
was then transported to another hospital for a liver trans-
plant. 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 
her enteral feeding was reduced to 100 calories/kg/day. At that visit, red cell galactose-1-phosphate was measured (table 2). Despite her liver transplant, patient B 
continued to show progressive liver failure and the report 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 con-
firmatory test, 4 years later, indicated no GALT activity.

Patient A is an example of new born screening hav-
ing a major positive impact upon the life of a child. 
Concomitantly, patient B exemplifies a pitfall of the new-
born screen. Paediatricians must be aware that inappropri-
ate 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 
transfusion. If galactosaemia is a consideration, it is 
prudent to introduce low lactose/galactose soy milk to 
the diet until the diagnosis can be confirmed later with 
the child’s native red blood cells.

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weight(kg)</th>
<th>RBC gal-1-P (µg/g Hgb)</th>
<th>Urine galactitol (µM/mM creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9.73</td>
<td>74 (68–125)</td>
<td>254.6 (194–620)</td>
</tr>
<tr>
<td>B</td>
<td>18.9</td>
<td>84 (80–125)</td>
<td>126.7 (194–620)</td>
</tr>
</tbody>
</table>

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 Hgb and normal urine galactitol is <45.4 µM/mM creatinine. Of: RBC, red blood cell.

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 con-
firmatory test, 4 years later, indicated no GALT activity.

DISCUSSION

The initial screening test results for each of these children 
suggested a defect in GALT activity. In patient A, the con-
firmatory test was performed after two exchange trans-
fusions; the results indicated normal GALT activity. The 
progressive liver failure in patient A responded to a lac-
tose-free diet making the clinical diagnosis of galactosaem-
ia likely. Six months after the exchange transfusions, the

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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