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 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 fluorescence 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 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 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.

Table 1 Patient A liver function

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

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

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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 fluid
s) 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
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 diarr-
hea that were attributed to milk protein allergy. Cow
milk was removed from her diet.

After patient A was diagnosed with classical galactosa-
emia, patient B (4 years old) had her red cell GALT activ-
ity 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 large
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-phos-
phate 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 diarrhea in associa-
tion with dietary lactose.

**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-
usions; the results indicated normal GALT activity. The
progressive liver failure in patient A responded to a lact-
ose-free diet making the clinical diagnosis of galactosaem-
ia 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 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 a
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 (80–125)</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/g Hgb and normal urine galactitol is <45.4 µM/mM creatinine. RBC, red blood cell.

**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.

**REFERENCES**
