

Positive neonatal screening for cystic fibrosis in neonates with renal failure

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ABSTRACT

Screening for cystic fibrosis (CF) was recently added to the neonatal screening programme in the Netherlands. Four patients with renal failure whose heel prick tests were positive for CF as defined by raised levels of immunoreactive trypsinogen (IRT) and pancreatitis-associated protein (PAP) are described. Both cystic fibrosis transmembrane conductance regulator (CFTR) DNA analysis and sweat tests were negative. Limited renal function can be a cause of false positive neonatal screening for CF using IRT and PAP.

INTRODUCTION

Screening for cystic fibrosis (CF) in neonates prevents growth delay,¹ reduces treatment intensity² and improves lung function.¹ In January 2008 a pilot study of CF screening was incorporated into the neonatal screening programme in the Netherlands. The CHOPIN trial compares two screening strategies for CF: serum immunoreactive trypsinogen (IRT) plus cystic fibrosis transmembrane conductance regulator (CFTR) DNA analysis vs serum IRT plus pancreatitis-associated protein (PAP).³ IRT is measured in all newborn infants. When the IRT level is raised (>50 µg/l), DNA mutation analysis is performed and PAP is determined. A sweat test is performed when IRT is >100 µg/l and PAP >1.0 µg/l, or when IRT is >50 µg/l and PAP >1.8 µg/l, or when DNA analysis reveals two CF-causing mutations.

We report on four patients with positive CF screening tests and renal failure.

CASE REPORTS

Patient 1 was born following a pregnancy complicated by maternal psychotic depression which required medication during the last week of pregnancy. The parents were Caucasian and unrelated. A balanced trisomy of chromosomes 13 and 14 of maternal origin had been diagnosed antenatally. The infant was born at term and had multiple dysmorphic features; a laryngeal web and an atrial septum defect were also found. He tested screen-positive for CF on the heel prick test performed on day 5 after birth. Subsequent CFTR DNA analysis and sweat test were negative (table 1). At the age of 3 weeks renal was noted. Ultrasound investigations revealed a multicystic dysplastic left kidney and a hyperechoic right kidney. At 19 months of age, height and weight are adequate for age with tube feeding.

Patient 2 was diagnosed antenatally with severe bilateral hydronephrosis. He was one of a twin

pregnancy and of mixed Caucasian and Caribbean ancestry. The mother had gestational diabetes. A caesarian section was performed at 35 1/7 weeks gestation for oligohydramnion. Birth weight was 1780 g (p5–10). Postnatally he required continuous positive airway pressure and developed a right-sided pneumothorax. He was diagnosed with posterior urethral valves and received bilateral ureterocutaneostomies. The heel prick test performed on day 6 after birth was screen-positive for CF. CFTR DNA analysis and sweat test were normal (table 1). He has shown good catch-up growth on tube feeding. Currently aged 18 months, he has end stage renal failure.

Patient 3 is the child of non-consanguineous North African parents. He had been diagnosed antenatally with a transposition of the great arteries for which he was admitted after birth. On day 2 after birth he was started on intravenous antibiotics for sepsis-like symptoms. Mild renal failure ensued secondary to diuretics and high levels of gentamicin which was still present at the time of newborn screening (day 5 after birth). Serum IRT and PAP levels were raised but the sweat test and CFTR DNA analysis were unremarkable (table 1). Kidney function has since much improved.

Patient 4 was conceived by in vitro fertilisation and is the first child of Caucasian parents. He was admitted at the age of 3 weeks for failure to thrive. On admission, renal failure was noted. He had posterior urethral valves, a non-functioning left kidney and severe right-sided hydronephrosis. He was also diagnosed with retrognathia and atrial septum defect type II. He underwent urethral valve ablation but required a ureteric stoma for sufficient renal drainage. The heel prick test performed on day 5 after birth was abnormal. A sweat test was attempted three times but yielded insufficient material for analysis. CFTR DNA analysis was negative (table 1). With tube feeding he has achieved good catch-up growth and is thriving well.

DISCUSSION

This is the first report of positive neonatal screening for CF in neonates with renal failure using IRT and PAP. Raised IRT levels have a low specificity for pancreatic disease,^{4 5} and even the first publication on the diagnostic value of IRT reported raised levels in patients with chronic renal failure.⁴ Following glomerular filtration, IRT is catabolised by the tubular apparatus.⁶ IRT levels are therefore raised in patients with a decreased glomerular filtration rate,^{5–7} and this is evident even in patients with mild renal impairment.⁷

Not unlike IRT, PAP is a small molecule of weak charge and is presumably readily filtered by the

Table 1 CFTR neonatal screening results, serum creatinine levels closest in time to newborn screening and sweat test chloride levels

| Patient | IRT ($\mu\text{g/l}$) | PAP ($\mu\text{g/l}$) | CFTR DNA | Creatinine ($\mu\text{mol/l}$) | Chloride (mmol/kg) |
|---------|-------------------------|-------------------------|----------|----------------------------------|--------------------|
| 1 | 79 | 6.4 | Negative | 115 | 25 |
| 2 | 71 | 2.0 | Negative | 426 | 7 |
| 3 | 113 | 1.3 | Negative | 94 | 10 |
| 4 | 65 | 2.6 | Negative | 195 | NA |

CFTR DNA, cystic fibrosis transmembrane conductance regulator DNA mutation analysis; IRT, immunoreactive trypsinogen; NA, not available; PAP, pancreatitis-associated protein.

glomerulus. One study reported raised PAP levels in patients on dialysis and kidney transplant recipients.⁸ Although the patients did not have pancreatic disease, some degree of pancreatic affliction could not be ruled out.

The presence of renal failure in our patients obviously does not rule out a diagnosis of CF. Sweat tests yielded chloride levels ≤ 30 mmol/kg in three of the patients, making a diagnosis of CF very unlikely.⁹ Subsequent CFTR DNA analysis was negative in all cases (a full description of the CFTR mutation analysis is given in the online supplement). As this analysis evaluates the presence of the 36 most common mutations in the Netherlands, it may have lacked sensitivity given the foreign ancestry of patients 2 and 3. Nevertheless, when the sweat test and CFTR DNA analysis are negative, no follow-up for CF is required.⁹ To date, no patient has developed symptoms compatible with CF. In view of the above, we have ascribed the positive screening results for CF in our patients to the presence of renal impairment at the time of heel prick testing. We advise that positive screening results for CF using IRT and PAP in patients with renal failure be interpreted cautiously, otherwise positive results in neonates with a subsequent negative sweat test and DNA results may be found in children with impaired kidney function.

Competing interests None.

Patient consent Obtained.

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