

# A seven-month-old girl with sweaty feet

Concerns often arise over a child's growth in the first year of life. If the child shows otherwise normal development and appears to be thriving, GPs and health clinics will try providing advice on diet and feeding routines. However, contented children may also have an underlying disease, and it is therefore standard practice to refer those with a flattening growth curve to the local paediatric department.

*A seven-month-old girl was referred by her GP for assessment owing to a flattening growth curve and hyponatraemia. The girl was born at full term following an uncomplicated pregnancy and delivery; birth weight was 3.6 kg. However, from two months of age she had not followed her weight-for-age curve and had fallen from the 50<sup>th</sup> percentile to below the 3<sup>rd</sup> percentile.*

*Her psychomotor skills were considered age-appropriate and she was contented and active. Her family was in good health, she had been vaccinated without notable reactions to the vaccines, and her newborn screening had been unremarkable. She had been breastfed from birth and breast milk was still her main source of nutrition. She had experienced silent reflux as an infant, but had not had significant diarrhoea or vomiting prior to admission.*

*The girl's parents reported that she sometimes smelled of sweat, especially her feet. She had been ill a number of times with fever and respiratory infections, but always relatively briefly and without complications. A stool sample at admission revealed adenovirus. Chest X-ray showed no opacities. The clinical examination was normal, with blood pressure 100/65 mm Hg and temperature 37.2 °C.*

*Blood tests revealed hypokalaemic metabolic alkalosis with hyponatraemia and hypochloraemia: pH 7.49 (7.35–7.45), pCO<sub>2</sub> 6.5 kPa (4.7–6.0 kPa), base excess [BE] 11.9 mmol/l (–3 to +3 mmol/l), HCO<sub>3</sub> 36.6 mmol/l (22.0–26.0 mmol/l), sodium 128 mmol/l (137–145 mmol/l), potassium 3.1 mmol/l (3.6–4.6 mmol/l), chloride 82 mmol/l (98–107 mmol/l). She received supplemental sodium chloride and potassium chloride as well as food via a nasogastric tube.*

It is important to exclude endocrine causes of hyponatraemia in infants as ignoring these may have fatal consequences. The mineralocorticoid aldosterone, which is produced in the adrenal cortex and has special receptors for sodium regulation in the renal tubules, is essential for regulating the salt

balance. Excess aldosterone leads to increased reabsorption of sodium in exchange for potassium, which is excreted in the urine.

Persistent hypokalaemia leads, via complex mechanisms, to increased bicarbonate reabsorption and acid excretion. Hyperaldosteronism is therefore associated with hypokalaemic metabolic alkalosis and hypertension (1). Due to accompanying fluid retention, the sodium excess will not usually be visible in blood tests. Rare conditions such as variants of congenital adrenal hyperplasia (CAH) (caused by 11 $\beta$ -hydroxylase or 17 $\alpha$ -hydroxylase deficiencies) and Liddle's syndrome (uninhibited sodium reabsorption in the renal tubules) are associated with hypokalaemic metabolic alkalosis and salt retention that may present in infancy.

Hyponatraemia of endocrine origin is usually associated with metabolic acidosis and hyperkalaemia; examples include classic congenital adrenal hyperplasia (with 21-hydroxylase deficiency), hypoaldosteronism, pseudohypoaldosteronism types I and II, and transient pseudohypoaldosteronism (2).

*Endocrine test results were completely normal: glucose 5.2 mmol/l, cortisol at 8:00 am and 8:00 pm: 393 nmol/l and 444 nmol/l respectively (28–938 nmol/l – children under two years of age are not expected to show the diurnal variation apparent in older children and adults), adrenocorticotrophic hormone (ACTH) at 8:00 am and 8:00 pm: 2.08 pmol/l and 3.13 pmol/l respectively (2–11 pmol/l), thyroid stimulating hormone (TSH) 2.03 mU/l (1.1–8.2 mU/l) and free T<sub>4</sub> 18 pmol/l (9.2–25.3 pmol/l).*

*Aldosterone and renin activity were undetermined at this point. Ultrasound and CT of the kidneys and adrenal glands showed normal morphology. Despite adequate nutrition and supplemental sodium chloride and potassium chloride, it took a week for serum electrolyte levels to normalise.*

Metabolic alkalosis with salt depletion may suggest kidney disease. In the kidney disease

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Bartter's syndrome, impaired reabsorption of chloride in the renal tubules leads to salt loss in the urine, hyponatraemia and hypokalaemic metabolic alkalosis. The salt loss causes secondary hyperaldosteronism and increased renin activity; blood pressure however is usually normal.

At least five genetic mutations are implicated in Bartter's syndrome, all with recessive inheritance. Symptoms of antenatal Bartter's syndrome emerge in utero, with polyhydramnios, preterm birth and a potentially fatal disease course owing to massive salt and fluid loss, hypercalciuria and development of nephrocalcinosis. Classic Bartter's syndrome presents in early childhood with failure to thrive, hypokalaemic metabolic alkalosis, polyuria and urinary salt loss.

*Given the possibility of electrolyte loss in the urine, a urine sample was obtained before the girl received supplemental salts. However, urinary electrolyte levels were normal considering the low serum levels of the same electrolytes (u-sodium < 20 mmol/l, u-chloride < 20 mmol/l, u-calcium 1.47 mmol/l, u-potassium 22 mmol/l). The urine was checked again a few days later and still showed low salt content.*

No endocrine or nephrological condition that we were aware of could explain the persistent metabolic alkalosis in the absence of urinary salt loss. Bartter's syndrome causes a metabolic hypokalaemic alkalosis but salt loss through the urine is obligatory. Salt loss via the gastrointestinal tract was also unlikely given that the girl had not had severe vomiting or diarrhoea.

*Faecal elastase was measured to exclude malabsorption, and was found to be normal at > 500 µg/g (> 200 µg/g).*

The results of the girl's newborn screening had been completely normal, and the normal elastase level ruled out pancreatic insufficiency too. But could the parents' comment that the girl often smelled of sweat be relevant to the diagnosis?

*A sweat test with measurement of skin conductance showed pathological results: 69–73 mmol/l, but the machine displayed an error message. Genetic testing revealed sequence variants in the CFTR gene in p.F508del, and in p.R117C in TRANS, consistent with phenotypic cystic fibrosis with preserved pancreatic function. A new sweat test was performed with specific measurement of chloride content, with results of 28 mmol/l and 38 mmol/l, mean 33 mmol/l (< 29 mg/l normal, 30–59 mmol/l uncertain, ≥ 60 mmol/l pathological).*

*A retrospective review of the child's newborn screening showed immunoreactive trypsinogen (IRT) of 39.5 ng/ml, i.e., a normal level. The results of aldosterone and renin activity tests subsequently became available: renin > 117.2 nmol/l/h (< 28.5 nmol/l/h, personal correspondence, Hormone Laboratory, Aker); aldosterone 2 740 pmol/l (164–2 929 pmol/l) (3). Thus, although the results of the child's newborn screening had been normal with respect to cystic fibrosis, the disease was nevertheless diagnosed on the basis of genetic testing, sweat tests and the medical history.*

## Discussion

Hyponatraemia is not uncommon in children under one year of age with an infectious disease, in part due to the low sodium content of breast milk/formula. Salts may also be lost via sweat, phlegm, vomiting and diarrhoea. Management of respiratory distress, better nutrition and treatment of the underlying infection often improves hyponatraemia without any further intervention being required. The girl's blood tests revealed hypokalaemic metabolic alkalosis with hyponatraemia and hypochloraemia. Metabolic alkalosis is seen frequently in children subject to severe vomiting. However, pyloric stenosis, for paediatricians the classic hypochloraemic alkalosis, was highly unlikely because the girl was more than six months of age and had not had projectile vomiting.

Pseudo-Bartter's syndrome is a condition that imitates classic Bartter's syndrome with hypokalaemic metabolic alkalosis, but where there is no renal tubule pathology and therefore no renal salt loss. When pseudo-Bartter's syndrome is suspected, it is important to investigate other possible causes of metabolic imbalance. Causes of pseudo-Bartter's syndrome include loss of chloride via the stools, via the stomach contents (cyclical vomiting) and via the skin (cystic fibrosis).

Pseudo-Bartter's syndrome is associated with cystic fibrosis. Young children who are breastfed or given formula are particularly prone to hyponatraemia, owing to the low salt content of the milk. Additional factors that may contribute to the development of pseudo-Bartter's syndrome are fever, the season, and a delayed diagnosis of cystic fibrosis. In Spain, the prevalence of pseudo-Bartter's syndrome in children with cystic fibrosis is 16.8% (4). There is reason to believe that the condition may be underdiagnosed in children with cystic fibrosis in Norway. However, southern European countries have a different climate, and the heat may contribute to development of the condition.

In healthy individuals, increased sweating leads to an adjustment of the sodium and chloride content of sweat, but in patients with cystic fibrosis, increased sweating may lead to excessive salt loss and vascular collapse (5). The loss of sodium and chloride produces extracellular hypovolaemia, which in turn leads to renin activation in the juxtaglomerular apparatus of the glomeruli, and hence activation of the renin-angiotensin-aldosterone system (RAS) and secondary hyperaldosteronism. Increased aldosterone leads to increased potassium loss in both sweat and urine, and thus hypokalaemia (5). The patient's high plasma renin activity and normal aldosterone level can perhaps be explained by the fact that low serum potassium can downregulate aldosterone release (6).

It is important to take hyponatraemia in children with cystic fibrosis seriously, as normalisation of blood sodium chloride through supplements may reduce renin activity. Children with cystic fibrosis may also have normal serum sodium, but nevertheless show activation of the renin-angiotensin-aldosterone system as a result of sodium depletion and hypovolaemia (7).

Sodium is an important growth factor in a child's first year of life, and hyponatraemia is probably a late sign of sodium depletion in children with cystic fibrosis. In Norway, general recommendations for the management of cystic fibrosis do not include the preventative use of oral salt supplements beyond the first year of life. However, salt supplements are recommended in the event of increased sweating. Hyponatraemia as part of pseudo-Bartter's syndrome should also be actively corrected in children with cystic fibrosis (7). Spot urinary sodium levels < 20 mmol/l and serum hyponatraemia indicate a clinically relevant sodium deficiency.

On 1 March 2012, newborn screening in Norway was expanded from two to twenty-three conditions, including cystic fibrosis. Screening for cystic fibrosis consists of measuring immunoreactive trypsinogen (IRT) in blood obtained via a heel prick in the period 60–72 hours after birth. At the time our patient was tested, the threshold for a positive test was an IRT level > 59.5 ng/ml. All blood samples with elevated IRT levels are then tested for mutations in the CFTR (cystic fibrosis transmembrane regulator) gene. Children with an elevated IRT level and two pathogenic CFTR mutations are reported as screen positive and proceed to cystic fibrosis diagnostics at Oslo University Hospital or Haukeland University Hospital (8).

The CFTR gene is located on chromosome 7 and encodes the CFTR protein, which is expressed on epithelial cells,

mainly in exocrine glands. The CFTR protein functions essentially as a chloride channel but also inhibits epithelial sodium transport and calcium-activated chloride channels, and is involved in bicarbonate-chloride-exchange. Impaired bicarbonate release leads to reduced solubility of glycoproteins in secretions, with the result that the secretions become highly viscous.

Exocrine glands are found in the skin and the intestines, as well as in the pancreas, lungs, bile ducts and genitalia. In the lungs, viscous mucus obstructs the airways, predisposing individuals to infection and inflammation, which over time leads to tissue destruction and fibrosis. In the pancreas, viscous secretions also obstruct the exocrine excretory ducts; the resulting enzyme deficiency leads to reduced metabolism of fats, and thus malnutrition. Between 85 and 90% of children with cystic fibrosis develop pancreatic insufficiency. Over time, patients may also develop cystic fibrosis-related diabetes mellitus (CFRD). Viscous secretions may additionally block the bile ducts; with increased inflammation this may eventually lead to biliary cirrhosis in older children and adolescents. Viscous secretions also affect intestinal motility, so that the patient may have both diarrhoea and constipation, and in newborns meconium ileus is virtually pathognomonic for cystic fibrosis. Infertility is very common in men with cystic fibrosis, partly due to impaired development of the vas deferens. Most women with cystic fibrosis are fertile, however, and it is less clear how female fertility is affected. Survival has improved greatly in recent years due to early diagnosis, active treatment, new medications and lung transplants.

Cystic fibrosis is a progressive multi-organ disease, but life expectancy is now over 40 years (9). The incidence in Norway is estimated at 1 in 5 600 newborns. Inheritance is autosomal recessive, and approximately 3% of the population in Norway are carriers of the disease. In Norway today there are just over 300 persons with cystic fibrosis, which makes it the country's most prevalent severe hereditary autosomal recessive disease.

Prior to the diagnosis of this child, there had been no reports in Norway of children with false-negative screening results for cystic fibrosis. Approximately 120 000 newborns in the country underwent screening during the programme's first two years. Over the course of these two years, 25 children tested positive on the basis of an elevated IRT level at screening and two *CFTR* mutations. Only isolated cases of false-negative screening due to a low IRT level have been reported internationally (10–12). None of

the children reported had meconium ileus, which is known to be associated with low IRT levels (13). For this reason all newborns with meconium ileus should undergo genetic testing for cystic fibrosis.

The sensitivity of screening based on IRT measurement and multiple *CFTR* mutations is estimated to be as high as 95.8–96.2% (10, 14). And yet one must always bear in mind that screening will not identify all those affected. It is important that doctors who were trained after cystic fibrosis was included in the screening programme are aware of the typical symptoms of the condition. Moreover, many children growing up in Norway today come from countries without screening programmes.

When frequent respiratory infections are accompanied by persistent infiltrates on chest X-rays and bronchiectasis, cystic fibrosis springs readily to mind. However, there are many other signs that should also raise suspicion of the condition: meconium ileus, cholestasis, steatorrhoea (due to pancreatic insufficiency), deficiency of fat-soluble vitamins, recurrent or chronic pancreatitis, failure to thrive, calcifications in the abdomen or scrotum, nasal polyps, chronic pansinusitis, pseudomonas in respiratory secretions, absence of the vas deferens, salty skin and, as in this patient, hypochloreaemic alkalosis without urinary salt loss (9).

This girl received a rapid diagnosis due to systematic assessment despite testing negative at newborn screening. The admitting doctor remembered to measure urinary electrolytes before the child was given substitution treatment, which simplified and shortened the investigation. The case illustrates that it is still important to consider cystic fibrosis whenever there are symptoms consistent with the condition, even in children who tested negative at newborn screening.

*The child's parents have consented to the publication of this article.*

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