CASE REPORT

Recurrent episodes of unexplained hyponatraemia of a rare cause in a young Saudi girl

Mohsen Suliaman Al-Atawi, Sulaiman Abdullah Al-Queflie,
Hamad Abdullah Al-Sadoon

Department of Pediatric, King Abdulaziz Medical City, Riyadh, Central Region, Saudi Arabia

Correspondence to
Dr Mohsen Suliaman Al-Atawi,
atawim@ngha.med.sa

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SUMMARY

We report a case of a 36-month-old Saudi girl who presented with recurrent episodes of unexplained hyponatraemia. Her cystic fibrosis CFTR (Cystic Fibrosis Transmembrane conductance Regulator) full gene sequence confirmed that she was homozygous for D579G mutation.

BACKGROUND

Cystic fibrosis (CF) is a relatively common autosomal recessive disorder. Its prevalence varies from country to country and with ethnic background; for example, the disease occurs in roughly 1 in 3000 white Americans, 1 in 4000–10 000 Latin Americans and 1 in 15 000–20 000 African Americans.^{1 2} It is uncommon in Africa and Asia, with a reported frequency of 1 in 350 000 in Japan.³ CF is caused by mutations involving the CFTR (Cystic Fibrosis Transmembrane conductance Regulator) gene.⁴

CFTR is involved in the absorption of NaCl by many epithelial cells, including sweat glands, where the process simply follows the classic model of salt absorption by epithelia involved in hypertonic absorption. Na⁺ and Cl⁻ ions enter the cell via ENaC and CFTR channels in the apical membrane (APM). Intracellular Na⁺ is pumped out by the Na⁺/K⁺ pump in the basolateral membrane (BLM). Cl⁻ diffuses out of the cells through basolateral CFTR Cl⁻ channels.⁵ It has also been shown that the CFTR anion channels are absent in both the BLM and APM of sweat ducts isolated from patient with CF. Lack of functional expression of CFTR prevents the exit of Cl⁻ across the BLM of CF cells.⁶ In addition, absence of CFTR in the APM of CF cells prevents lumen-to-cell Cl⁻ diffusion and causes significant depolarisation (makes the membrane more positive) of the APM potential. APM depolarisation abolishes the electrical driving force and prevents passive diffusion of Na⁺. As a consequence, both Na⁺ and Cl⁻ ions are retained in the lumen, causing significant loss of electrolytes during sweating, particularly in patients afflicted by overheating. Thus, elevated sweat NaCl concentration is the basis of the classic pilocarpine-induced sweat test as a diagnostic feature of CF disease.⁷

Worldwide, the most common mutant allele is the delta F508 mutation, which is a three-nucleotide deletion of a phenylalanine residue.⁸ This mutation is responsible for approximately

two-thirds (66%) of all CF chromosomes followed by less common but important mutations in the remaining one-third of all alleles, depending on population and geographical location, such as: G542X (2.4%), G551D (1.6%), N1303K (1.3%), W1282X (1.2%), 3120+1G→A (1%), R553X (1%), 621+1G→T (1%), 1717-1G→A (1%), 3849+10kbC→T (1%), 2789+5G→A (1%).^{2 9-11}

The clinical presentation of CF is based on the type of mutation involving the CFTR gene, hence there is a strong genotype–phenotype correlation.¹² Individuals with classical CF usually present with characteristic clinical features (discussed below) making the diagnosis of CF straightforward, however, this is not the case when faced with rare, non-classical types of CF, which may be difficult to diagnose and frequently missed. The incidence of CF in Saudi Arabia was reported to be 1 in 4243 children, with the following mutations most commonly reported in descending frequency: 1548delG (18%), I1234V (16%), 3120+1G→A (9%), H139 L (6%), ΔF508 (6%), N1303K (5.4%), W1282X (4.3%), 711+1G→A (3%), G115X (3%), S549R (3%), 4010del4 (2.2%).¹³⁻¹⁵

In this report, we discuss a young Saudi girl who presented with repeated but ‘unexplained’ electrolyte disturbances, who was diagnosed as having a very rare type of non-classical CF, based on full sequence testing for the CFTR gene.

CASE PRESENTATION

We present a case of a 36-month-old Saudi girl, a product of a consanguineous marriage, who was repeatedly admitted to hospital due to recurrent episodes of dehydration and electrolyte disturbances. In her latest admission at the age of 36 months, the patient presented to our paediatric emergency room with a 4-day history of fever with decreased oral intake; her fever was responsive to acetaminophen. On physical examination, she was found to have a mild degree of dehydration but she was not pale or cyanosed. Her growth parameters were: weight 13.7 kg, height 92 cm; both at the 25th centile for age and sex. Her vital signs were: temperature (tympanic) 36.8°C, pulse 80 bpm, blood pressure 88/48 mm Hg (at 25th centile for age and sex and height). Her pulse oximetry saturated around 96% on room air. Ear-nose-throat (ENT) examinations revealed bilaterally moderate injected tonsils, with no follicles, pus or membranes, and her ears and nose were normal. Chest

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examination revealed a normal chest with adequate and equal expansion and normal breath sounds with no wheezing. The remainder of her physical examination was unremarkable.

Her neonatal and medical history revealed that she had passed her meconium in the first few hours after birth and was discharged with her mother in good clinical condition 1 day later. She had been admitted twice, at 7 and 12 months of age, because of dehydration and electrolyte disturbances; both admissions were due to upper respiratory tract infection resulting in inadequate oral intake. Worth mentioning is that she had no history suggestive of failure to thrive, and no recurrent chest problems such as coughing, wheezing or difficulty breathing. Her developmental milestones were compatible with her chronological age and her family history was negative for similar cases.

Her initial clinical diagnosis was of moderate sore throat, and mild dehydration with electrolyte disturbances.

INVESTIGATIONS

The patient's initial investigations conducted in the emergency room revealed hyponatraemia (Na=130 mmol/L), hypokalaemia (K=2.8 mmol/L) and hypochloraemia (Cl=90 mmol/L) along with metabolic alkalosis. Her urinary electrolytes before intravenous fluid therapy showed that urinary sodium and potassium were both <20 mmol/L.

Table 1 below summarises the patient's three hospital admissions along with selected laboratory findings for each admission. Of interest, the patient's sweat chloride test result was reported as borderline, however, her full CFTR gene sequence confirmed that she had a homozygous D579G mutation.

TREATMENT

During her admission, the patient received intravenous fluid with electrolyte replacement.

She was discharged on regular supplementation of oral sodium chloride.

OUTCOME AND FOLLOW-UP

The patient was kept on oral supplementation of sodium chloride and her mother was instructed to give the child liberal fluid orally during her sickness. Since then there have been no

further hospital admissions and the family has been referred for genetic counselling.

DISCUSSION

The clinical presentation of CF is highly heterogeneous among individual patients, even among siblings carrying identical CFTR mutations.

Patients with classical CF have characteristic clinical features, for example, in the neonatal period, they may present with delayed passage of meconium (>24–48 h), early onset of respiratory difficulties, meconium ileus (10–15%) and prolonged cholestatic jaundice, and in early infancy, CF manifestations include large volumes of stools, oily stools (steatorrhoea), failure to thrive, and chronic or recurrent cough and wheezing. Our case lacked these characteristic clinical features of classical CF in the neonatal period and in her early infancy; had any of these features been present, they might have facilitated an earlier diagnosis of her condition. She presented with repeated yet unexplained hyponatraemia in her third admission; we carefully tested and evaluated the three more common routes for fluid and electrolyte loss, namely, the gastrointestinal tract, renal system and, finally, the skin sweat ducts as a rarer but possible route for such losses. The lack of vomiting and diarrhoea in each of the patient's three admissions readily excluded the gastrointestinal tract as a possible route; the lack of excessive urination along with low urinary electrolytes (sodium and potassium) further excluded her renal system; so the remaining possible route was her sweat ducts. Furthermore, the presence of varying degrees of metabolic alkalosis instead of the anticipated metabolic acidosis pointed to the fact that this patient had chronic potassium depletion through her sweat ducts.

In fact, it was the unique combination of hyponatraemic dehydration and the presence of varying degrees of metabolic alkalosis, in the absence of clear and visible water and salt loss, that directed us to search vigorously for the possibility of CF.

Our case also addresses the need to include this rare form of non-classical CF in the differential diagnosis for this peculiar presentation in any paediatric patient presenting with recurrent but unexplained episodes of dehydration and electrolyte disturbances, even though CF is considered a rare disorder in our country.

Table 1 Laboratory findings

Laboratory tests	Laboratory reference range	First admission (age 7 months)	Second admission (age 12 months)	Third admission (age 38 months)
Blood urea nitrogen (mmol/L)	1.8–6.0	10.5	7.1	8.7
Serum sodium (mmol/L)	138–145	129	132	130
Serum potassium (mmol/L)	3.4–4.7	2.6	3	2.8
Serum chloride (mmol/L)	95–110	73	93	90
Serum creatinine (μmol/L)	27–62	37	36	40
Blood sugar (mmol/L)	3.3–5.6	5.6	4.7	5.5
Carbon dioxide (mmol/L)	20–28	38	28	33
Urine sodium (mmol/L)	–	–	–	<20
Urine potassium (mmol/L)	–	–	–	<20
Sweat conductivity (mmol/L)		Not performed	Not performed	72
<60 is normal				
Between 40 and 80 is borderline				
More than 80 is abnormal				
Sweat chloride (mmol/L)		Not performed	Not performed	52
<40 is normal				
Between 40 and 60 is borderline				
More than 60 is abnormal				

Our patient's 'full' CFTR gene sequence confirmed that she had a homozygous D579G mutation. To the best of our knowledge, this is the first case of this type of CF mutation to be reported from Saudi Arabia and the second case in the paediatric literature addressing the need to test for a full gene sequence in patients suspected of having CF.

Homozygous D579G mutation is considered to be a very rare type of non-classical CF; this type of mutation has been reported mainly from Italy, particularly from the Puglia area,^{16 17} and was first reported by Brancolini *et al*¹⁶ in two pancreatic-sufficient patients with variable lung insufficiency. In 1999, Picci *et al*¹⁸ identified the first adult homozygous patient carrying a D579G mutation. The patient was a young fertile woman who presented with a chronic cough and sinusitis starting at the age of 20 years; she was found to have very mild pulmonary disease with no evidence of pancreatic or hepatic involvement. In 2004, Salvatore *et al*¹⁹ reported the first case in the paediatric age group, of a boy who presented with dehydration and metabolic alkalosis.

Learning points

- ▶ Cystic fibrosis must be considered in patients with unexplained recurrent dehydration and metabolic alkalosis.
- ▶ D579G mutation, considered a very rare form of cystic fibrosis, must be included in the differential diagnosis of recurrent, unexplained hyponatraemic dehydration.
- ▶ D579G mutation is not limited to any particular geographic location or specific ethnic group.
- ▶ A full sequence of the CFTR (Cystic Fibrosis Transmembrane conductance Regulator) gene was required in our case to confirm our diagnosis.

Competing interests None declared.

Patient consent Obtained.

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