CASE REPORT

Syndromic congenital diarrhoea: new SPINT2 mutation identified in the UAE

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SUMMARY

We are reporting a new mutation in the SPINT2 gene (c.443G>A (p. Arg148His)) that explains the association of choanal atresia with congenital sodium diarrhoea (CSD) in an Emirati family in the Middle East. To our knowledge, this mutation is neither listed in a mutation database nor described in the literature. Similar to other patients with CSD associated with SPINT2, this child remains dependent on parenteral nutrition for fluids and nutritional support resulting in failure to thrive. The determination of the molecular basis of syndromic CSD will facilitate prenatal and postnatal diagnosis of patients and will contribute to counselling of affected families, especially in areas like the UAE where consanguineous marriages are not uncommon.

BACKGROUND

This patient has been identified as carrying a novel SPINT2 mutation c.443G>A (p. Arg148His) homozygous. This report adds to the list of disease gene mutations known to be associated with congenital sodium diarrhoea (CSD). This may be of specific relevance to the UAE where this mutation has been identified.

The patient described in this report was born to consanguineous parents (first cousins). This baby had bilateral choanal atresia. Within a few days of life, baby developed acute severe diarrhoea associated with metabolic acidosis. There was also a background history of death of a sibling with similar features. These phenotypic features in association with diarrhoea are recognised (based on literature review) to occur in children with a mutation of the SPINT2 gene.

CSD is a rare inherited cause of diarrhoea of infancy with two distinct types: classic CSD and syndromic CSD. The disease gene of the classic type is unknown; however, the disease gene of the syndromic CSD is a serine protease inhibitor, SPINT2. Five SPINT2 mutations have been described previously in the literature.

Recognising the existence of this condition (and where possible, the molecular diagnosis) within a family will assist earlier diagnosis in other children and assist in the initiation of life-saving treatments as the symptoms/complications become apparent.

CASE PRESENTATION

We describe a full term female (46XX) infant, delivered by caesarean section to a 42-year-old para 6, gravida 5, type 2 diabetic mother. The pregnancy

was complicated by polyhydramnios. There were no risk factors for neonatal sepsis identified at the time of birth. Parents are consanguineous (first cousins). There was no history of atopy. This baby was admitted to our neonatal intensive care unit with respiratory distress associated with bilateral membranous choanal atresia which was confirmed on CT scan. Birth weight was 2340 g (<5th percentile), length 45 cm (<5th percentile), head circumference 33 cm (<5th percentile).

Enteral feeding was initiated using expressed breast milk. On day 7 of life, the baby developed hypovolemic hyperchloremic shock due to acute non-bloody diarrhoea. The baby had sunken eyes, depressed anterior fontanelle and Kussmaul respiratory pattern. The baby had biochemical evidence of dehydration (hypernatremia, metabolic acidosis) and lost 21% of the birth weight (table 1). The baby was screened for sepsis and empirically commenced on antibiotics which were continued for 48 hours when the blood cultures were proven as sterile. By this time point, baby had shown dramatic response to the treatment measures (fluid resuscitation, correction of electrolytes and acid-base balance and bowel rest) that had been initiated to address the sudden clinical deterioration. Antibiotics were therefore discontinued.

Enteral feeds were cautiously initiated but were never fully achieved as it became quickly apparent that more than 5 mL of milk every few hours resulted in profuse diarrhoea. Parenteral nutrition (PN) became and continues to be the mainstay for fluid and nutritional support. Not surprisingly, central line infection, a recognised cause of morbidity (and mortality), has been a challenge.

In addition to bilateral choanal atresia, other abnormalities identified include duplex left kidney, hypertelorism and long philtrum (figure 1). Echocardiography and cranial ultrasound scans were unremarkable. Eye examination did not reveal corneal abrasion or keratitis.

The diagnosis of congenital diarrhoeal disorder (CDD) was considered following the development of profound dehydration due to an acute episode of diarrhoea when feeds were initiated. There was also history of polyhydramnios during this and the preceding pregnancy.

SPINT2 gene mutation was suspected as the underlying molecular diagnosis based on the well-described association of choanal atresia and renal anomalies with this disease gene.

PCR amplification was done with sequencing of all coding exons with adjacent intronic sequences

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Table 1 Significant weight loss, hypernatremia and metabolic acidosis secondary to severe diarrhoea that occurred on day 7 of life

Day of life	Weight (kg)	Sodium (mmol/L)	Potassium (mmol/L)	pH	Base excess	Chloride (mmol/L)	Bicarbonate (mmol/L)	Urea (mmol/L)	Creatinine (μmol/L)
1	2.34	133	4.4	7.4	−5	104	24		
3	2.1	142	4.8					1.2	56
7	1.85	154	6.8	7.229	−17	117	13	5.4	52
10	1.89	142	3.6	7.46	+10	97	32	3.8	33

of the SPINT2 gene (seven exons, Ref.seq.: NM_021102.3). Sequencing was performed with SeqPilot (JSI, Germany) which revealed that our patient is homozygous for the SPINT2 gene mutation: c.443G>A (p. Arg148His). The effect of this mutation is attributed to an amino acid change (the A in the start codon ATG in exon 1 represents the nucleotide position 1: p. Arg148His). As parents are consanguineous and have had a previous child with very similar features and clinical journey, we have assumed that both parents must be carriers of this disease gene.

The chromosome analysis revealed a female chromosome complement, 46 XX, without numerical and structural anomalies. A high-resolution microarray-based comparative genomic hybridisation analysis performed did not identify any abnormalities.

While these results were awaited, upper gastrointestinal endoscopy and biopsy (for electron microscopic study) were done in an attempt to identify other possible explanations of this baby's phenotypic and clinical presentation. Other differential diagnosis considered included microvillus inclusion disease and congenital tufting enteropathy. The biopsies taken were suggestive of villous atrophy, but electron microscopy did not identify any molecular abnormalities.

The presentation of this baby presented in this report was near identical to a previous pregnancy in 2013 that ended as late neonatal death at a postnatal age of 21 days. This baby, was born at 35 weeks' gestation, had bilateral choanal atresia and cloudy cornea. This baby developed profuse diarrhoea as a preterminal event.

Accession numbers

The GenBank accession number for the SPINT2 mRNA sequence reported in this paper is NM_021102.3.

Figure 1 The patient at 30 days of life with hypertelorism and a long philtrum, which are recognised features associated with SPINT2.

INVESTIGATIONS

- ▶ Blood culture: negative at 48 hours.
- ▶ Stool reducing substances: negative.
- ▶ Stool occult blood: negative.
- ▶ Stool culture: negative.
- ▶ Small bowel intestinal biopsy: villous atrophy.
- ▶ Stool electrolytes analysis
- ▶ Average weight per 24 hours 15 g (normal 80–200 g).
- ▶ Sodium 8.1 mEq/100 g, that is, 1.2 mEq/24 hours (normal 1–10 mEq/24 hours).
- ▶ Potassium 1 mEq/100 g, that is, 0.2 mEq/24 hours (normal 8–20 mEq/24 hours).

DIFFERENTIAL DIAGNOSIS

Based on the history and the age of the child, the following differentials were considered:

- ▶ neonatal sepsis
- ▶ milk intolerance/atopy
- ▶ malabsorption syndromes
- ▶ enteropathies such as microvillus inclusion disease and congenital tufting enteropathy.

TREATMENT

Baby was rehydrated intravenously and was given alkali infusions. She was commenced on total parenteral nutrition (TPN) within a few days of life once it became apparent that CSD/CDD was suspected as potential diagnosis. She remains TPN dependent. Curative treatments for this condition are unavailable.

OUTCOME AND FOLLOW-UP

Similar to other described cases linked to SPINT2 mutation, the patient (now aged 21 months) remains dependent on PN as she has frequent chronic diarrhoea. She tolerates small amount of feeds (semisolids) orally, the increment of which has been hampered by oral aversion to feeds. Not surprisingly, she is failing to thrive—weight (10 kg) and height (74 cm) are well below the 5th percentiles. Her gross motor development has been hampered by the dependence on PN (she is cruising around furniture) but she is socially appropriate. She has biochemical markers suggestive of liver disease (due to prolonged use of PN) and has had central line infections—both recognised causes of morbidity and mortality in children with CSDs. She remains under regular follow-up by gastroenterology, general paediatrics and speech and language therapy and her family has access to respite care.

DISCUSSION

CSD (MIM 270420), first described in 1985, is a rare inherited cause of diarrhoea of infancy due to defective sodium and hydrogen exchange.¹ There is a genetic mutation ascribed to the SPINT2 gene that has explained the syndromic form of the

disease.² The disease gene for the other form known as classic CSD has not been identified.

The disease gene of the syndromic CSD, SPINT2, was identified by Heinze *et al* (2009) using genome-wide single nucleotide polymorphism linkage analysis. They identified the following five distinct mutations (homozygous or compound heterozygous) in patients with syndromic CSD: p.Y163C, c.1A/T, c.337p2T/C, c.553p2T/A and c.593_1G/A. SPINT2 mutations were associated with loss of protein synthesis or failure to inhibit the serine protease trypsin *in vitro*.²

CSD is characterised by increased faecal sodium excretion, (faecal Na⁺ >70 mmol/L, normal 20–35 mmol/L); however, the effect of SPINT2 mutation on the faecal excretion of sodium remains unclear in cases of syndromic CSD.¹

Congenital secretory diarrhoea is an autosomal recessive disorder and is caused by mutation in the serine protease inhibitor, Kunitz type, SPINT2 gene. In our patient, PCR amplification was done with sequencing of all coding exons with adjacent intronic sequences of the SPINT2 gene (seven exons, Ref. seq.: NM_021102.3). Sequencing was performed with SeqPilot (JSI, Germany) which revealed that our patient is homozygous for the SPINT2 gene mutation: c.443G>A (p.Arg148His). The expected effect of this mutation is an amino acid change p.Arg148His which concerns a highly conserved amino acid. The *in silico* programs (SIFT, MutationTaster, PolyPhen) predict for this mutation a disease-causing effect. Furthermore, a mutation p.Arg148Cys, affecting the same amino acid position in SPINT2, is considered disease causing. This latter mutation was found compound heterozygous together with another SPINT2 mutation in two siblings with congenital tufting enteropathy, which is another type of congenital enteropathy.³ Based on these evidences, the SPINT2 mutation c.43G>A can be classified as highly likely disease causing. Assuming that c.443G>A is the pathogenic mutation located on both alleles, this report confirms the diagnosis of congenital secretory sodium diarrhoea in our patient.

Consanguinity and the ‘founder’ effect explain an increased incidence of CDD within families and/or within certain geographical areas.⁴ This is important in places such as the UAE where consanguineous marriages are not uncommon.

Intestinal biopsy with histological examination still has a place in making a diagnosis of CDDs.⁴ However, advances in molecular studies and close collaboration between physicians and

geneticists may spare the child from invasive tests and assist the paediatrician in managing this condition earlier in life.⁵

When CDDs are suspected, efforts should be made to make a molecular diagnosis and identify the disease gene which may facilitate prenatal diagnosis. This will have direct impact on antenatal and postnatal management of the child and family.

Learning points

- We are reporting, from the UAE, a new novel mutation within the SPINT2 gene (c.443G>A (p. Arg148His)).
- Congenital diarrhoeal disorders should be considered when babies present with unexplained severe diarrhoea following a pregnancy complicated by polyhydramnios.
- The presence of choanal atresia and severe diarrhoea should direct genetic testing towards the SPINT2 gene.
- Close collaboration between physicians and geneticists is required for optimal antenatal and postnatal care of an affected family.
- Advances in molecular studies may identify further mutations of this disease gene in the future in various geographical areas.

Contributors SBC initially saw the baby and did the literature review, got the consent from parents, wrote the case and obtained the photos. JDE and BNO were involved in the care of the baby, they reviewed the case and finally approved it for submission.

Competing interests None declared.

Patient consent Obtained from guardian.

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