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Case Series

# Enteroendocrine Dysfunction in Two Saudi Sisters

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## Keywords

Proprotein convertase 1/3 · Intractable diarrhea · Malabsorption · Congenital enteropathy

## Abstract

Proprotein convertase (PC) deficiency is a rare autosomal recessive disorder caused by mutations in proprotein convertase subtilisin/kexin type 1 (*PCSK1*). It is characterized by severe malabsorptive early-onset diarrhea, obesity, and systemic endocrinopathies. Only few cases have been reported in the literature; we have add two female sisters with some difference in clinical progress. Herein, we describe two sisters with congenital osmotic diarrhea diagnosed with PC1/3 deficiency, causing malabsorptive diarrhea and enteroendocrine dysfunction, who presented with chronic enteropathy with hypernatremia but with different expressivity. PC1/3 deficiency presents with symptoms and signs that mimic glucose-galactose malabsorption. Because of the clinical paucity and heterogeneity of congenital enteropathies, whole-exome sequencing may be of great help towards early diagnosis and effective treatment.

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## Background

Proprotein convertases (PCs) are a family of serine endoproteases responsible for the conversion of inactive propeptides into biologically active peptides [1]. Proprotein convertase subtilisin/kexin types 1 and 2 (*PCSK1* and *PCSK2*) are two endoproteases mainly expressed

in the secretory pathway of neuroendocrine tissues where they are involved in tissue-specific processing of prohormones and neuropeptide precursors, such as pro-opiomelanocortin, prothyrotropin-releasing hormone, proinsulin, proglucagon, and progonadotropin-releasing hormone [2–6]. PC1/3 deficiency is an autosomal-recessive disorder caused by mutations in *PCSK1*. The clinical manifestation of PC1/3 deficiency is characterized by malabsorptive diarrhea, polyphagia with obesity, and certain endocrinopathies, including growth hormone deficiency, adrenal insufficiency, central diabetes insipidus, hypothyroidism, and primary hypogonadism [7]. Obesity is caused by mild homozygous as well as heterozygous mutations of *PCSK1* [7–10].

The severe generalized malabsorptive diarrhea and malnutrition lead to increased mortality. Although systemic endocrinopathies evolve with age, the need for parenteral nutrition (PN) support decreases. Obesity, which is lessened by malabsorption, develops later in PC1/3 deficiency; however, enteroendocrine cell dysfunction is the principal underlying factor that leads to early clinical manifestation [7, 11, 12].

Sequencing of target genes, such as *NEUROG3*, *EPCAM*, and *MYO5B*, can be done based on histology or nutrient absorption characteristics in genetic diarrheal disorders [13–16]. However, clinical data in these rare congenital diarrheal disorders may not be sufficient for sequencing known genes. Thus, whole-exome sequencing (WES) can discover known and novel mutations in known as well as unsuspected genes in a manner that efficiently directs clinical care [11, 17, 18].

To date, 22 patients from 17 families with mutations involving *PCSK1* have been described. Herein, we report two female siblings with PC1/3 deficiency manifested by congenital osmotic diarrhea with hypernatremia.

## Case Reports

### Case 1

The index case is a 1-month-old female infant (currently 6 years old) who presented with profuse watery diarrhea 10–15 times per day since day 13 of life. She required admission to the pediatric intensive care unit in the local hospital for management of severe dehydration and hypotensive shock which was associated with severe metabolic acidosis and hypernatremia. Serum sodium was 160 mmol/L (normal 135–145 mmol/L), serum chloride 124 mmol/L (normal 98–107 mmol/L), serum bicarbonate 5 mmol/L (normal 18–24 mmol/L), serum potassium 2.8 mEq/L (normal 3.5–5.5 mEq/L), blood urea 3.4 mmol/L (normal 2.5–6.4 mmol/L), and serum creatinine 53  $\mu$ mol/L (normal 44–80  $\mu$ mol/L). After stabilization in the local hospital, the infant was referred to our institute because of persistent diarrhea of the same frequency and growth failure. She had been born by normal vaginal delivery at term, and the pregnancy had not been complicated by polyhydramnios. She ranked fourth in the family and the parents were second-degree cousins. Birth weight was 2.4 kg and length was 50 cm. Family history revealed an older sister who had presented 6 years earlier with the same clinical features. Physical examination on admission showed a weight of 2.5 kg and a length of 49 cm, both of which were below the third centile for age in the CDC growth chart. The abdomen was distended but without ascites or organomegaly. Serum electrolytes on admission revealed sodium 150 mmol/L (normal 135–145 mmol/L), potassium 3.6 mEq/L (normal 3.5–5.5 mEq/L), chloride 120 mmol/L (normal 98–107 mmol/L), magnesium 0.74 mmol/L (normal 0.70–1.05 mmol/L), phosphate 0.7 mmol/L (normal 1.1–2.2 mmol/L), calcium

2.6 mmol/L (normal 2.24–2.7 mmol/L), serum creatinine 19  $\mu$ mol/L (normal 44–80  $\mu$ mol/L), urea 11.9 mmol/L (normal 2.5–6.4 mmol/L),  $\text{HCO}_3^-$  11.4 mmol/L (normal 118–24 mmol/L), and albumin 34 g/L (normal 34–50 g/L). Other workup included tandem mass spectrometry and urine for organic acids, serum immunoglobulins, lymphocyte markers, blood culture, and abdominal ultrasonography; all came unremarkable. Fasting for >24 h resulted in complete cessation of diarrhea. The measured fecal osmotic gap was very high (214.2 mosmol/kg, normal 50–100 mosmol/kg; measured fecal sodium 13 mmol/L and potassium 24.9 mEq/L), indicating the osmotic nature of the diarrhea. Upper gastrointestinal endoscopy was done and the small intestinal biopsy was reported with villous atrophy with normal disaccharidase level. Genetic tests including *EPCAM*, *MYO5B*, and *NEUROG* came unremarkable. WES was conducted when it was available in our institute and revealed a homozygous mutation in *PCSK* (g.95735734\_95735737del, NM\_000439.4; c1350\_1353del; p.Asp451fs), confirming the diagnosis of PC1/3 deficiency. The patient was managed by PN therapy and early introduction of oral feeds. PN was successfully discontinued at the age of 1 year following significant improvement of diarrhea and weight gain. However, PN was reintroduced following relapse of symptoms and growth cessation. Currently PN is on hold (by the family) with deterioration of growth (weight 14.3 kg, height 102 cm, both below the 3rd centile in the CDC chart, and a BMI of 13.75; 10th centile). Additionally, she developed cortisol and growth hormone deficiencies and hypothyroidism (*PCSK1* insufficiency-associated endocrine abnormalities) since the age of 3.

### Case 2

Six years earlier, an older sister (currently 12 years old) had presented to our center at the age of 6 months with the same problems of profuse watery diarrhea 10–15 times per day which developed at the same sister's age. She required multiple pediatric intensive care unit admissions in the referring hospital because of dehydration and electrolyte disturbances in the form of high serum sodium and chloride, hypokalemia, and metabolic acidosis. On admission to our institute both weight and height were below the 3rd centile (weight of 2.6 kg and length of 50 cm). Systemic examination revealed severe wasting and abdominal distension, but there were no ascites, lower limb edema, or palpable organs. Serum electrolytes showed sodium 155 mmol/L (normal 135–145 mmol/L), potassium 2.5 mEq/L (normal 3.5–5.5 mEq/L), chloride 125 mmol/L (normal 98–107 mmol/L), magnesium 0.7 mmol/L (normal 0.70–1.05 mmol/L), phosphate 0.5 mmol/L (normal 1.1–2.2 mmol/L), calcium 2.1 mmol/L (normal 2.24–2.7 mmol/L), serum creatinine 55  $\mu$ mol/L (normal 44–80  $\mu$ mol/L), urea 7 mmol/L (normal 2.5–6.4 mmol/L),  $\text{HCO}_3^-$  10 mmol/L (normal 18–24 mmol/L), and albumin 30 g/L (normal 34–50 g/L). Metabolic tests, immune deficiency tests, infectious tests, as well as abdominal ultrasonography were unremarkable. Fasting for >24 h resulted in a complete resolution of diarrhea and fecal osmotic gap was significantly high (170 mosmol/kg; measured fecal sodium 45 mmol/L and potassium 15 mEq/L), confirming the osmotic nature of the diarrhea. Based on the clinical features of osmotic diarrhea, hypernatremia, and metabolic acidosis, which suggests glucose galactose malabsorption, administration of Galactomin 19 milk formula did not result in improvement. Upper endoscopy and small intestinal biopsy revealed mild villous shortening. Moreover, mutation analysis of *EPCAM* and *MYO5B* as well as autoimmune enteropathy workup were unremarkable. At the age of 6 years and based on her sister's diagnosis, targeted mutation for *PCSK1* was done and revealed the same sister's mutation. She did not require PN beyond the age of 11 months following gradual resolution of diarrhea and satisfactory weight gain. She has developed polyphagia and obesity (weight 53 kg [75th–90th

centile], height 143 cm [10th–25th centile in the CDC chart] and a BMI of 25.98 [>97th centile]), but no endocrinological symptoms hitherto.

## Discussion

This report describes the clinical pattern and genetic findings of two female siblings with PC1/3 deficiency, which was determined by WES. Generalized malabsorptive diarrhea, which is the early presenting feature, may be caused by impaired processing of prohormones secreted by enteroendocrine cells [7]. The early disease manifestations in our patients were severe diarrhea and failure to thrive. We found complete cessation of diarrhea upon fasting for >24 h, indicating its osmotic nature; however, other reports showed that fasting resulted in either a partial response or lack of improvement in diarrheal output [7, 19]. This report shows that PC1/3 deficiency can occur in females [20], although they have been underrepresented in other studies [7, 21].

It is thought that PCSK1 is largely needed only during early infancy to support the necessary high-caloric intake, which explains the successful discontinuation of PN after the first 18 months of life [7, 11, 12]. However, one of our patient did not tolerate weaning off PN, which necessitated reintroduction of PN after reemergence of chronic diarrhea, metabolic acidosis, and cessation of weight gain, after other causes of chronic diarrhea had been extensively excluded.

An important aspect of our approach was using WES in the workup of these two patients to identify the underlying molecular etiology, because it was proven to be an efficient and powerful diagnostic tool in diagnosing enigmatic and rare disorders [11]. Previous reports showed that small intestinal histology has no role in diagnosing PC1/3 deficiency [7]; the same was true for our patients.

Early-onset obesity combined with severe polyphagia has been described in PC1/3 deficiency [22]. The older patient in this report is gaining weight progressively, reaching a BMI of >97th centile; however, the younger patient's weight is fluctuating because of recurrence and persistence of her symptoms.

The youngest sister developed other endocrinological manifestations at an earlier age (3 years), namely hypothyroidism, adrenal insufficiency, and growth hormone deficiency for which the endocrinologist was involved in her management. However, the oldest 12-year-old sister has so far manifest neither of these associated endocrinopathies, though they might evolve later [7, 11, 12]. The difference in the clinical progress of the two sisters is possibly related to a difference in expressivity of the same mutation, with possible presence of a gene modifier.

In conclusion, PC1/3 deficiency should be considered in the differential diagnosis of osmotic and intractable neonatal diarrhea with hypernatremia and metabolic acidosis that mimic glucose-galactose malabsorption.

Some patients with PC1/3 deficiency may need long-term PN beyond infancy, which is dissimilar to what has been reported; therefore, a prospective multicenter study is warranted to further explore phenotypic-genotypic correlations.

Since PC1/3 deficiency is a rare disease, WES may be particularly helpful for the rapid and accurate diagnosis of congenital enteropathies because of the heterogeneity and paucity of clinical manifestations.

## Statement of Ethics

King Fahad Medical City Review Board (IRB) approved this case report study with IRB Log No. 17-165. The parents accepted publishing the case study, and as per the IRB policy, written consent is not required if there are no identifiers.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Both authors participated in the case report idea. A.B.M. Ahmed wrote the manuscript. Both authors participated in paper revision, reading, and final approval for publication.

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