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SCIENTIFIC LETTER

Proprotein Convertase 1/3 Deficiency

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To the Editor: Congenital diarrheal disorders (CDD's) are a rare entity caused by various recessively inherited mutations and typically manifest in early stages of life [1]. *Proprotein convertase subtilisin/kexin type 1 (PCSK1)* gene encodes for prohormone convertase 1/3 (PC1/3) responsible for peptide hormone processing within the enteroendocrine cell [2]. This enzyme activates multiple substrates including proglucagon, pro-insulin, and propiomelanocortin to their active metabolites [3]. PC1/3 deficiency leads to severe watery diarrhea, impaired growth in infantile period, and severe obesity and endocrinopathies *e.g.*, Growth Hormone (GH) deficiency, Diabetes Insipidus (DI) and hypogonadism if children survive the neonatal period [3]. We report two siblings who presented with severe diarrhea in the neonatal period and summarize their clinical features outlining the importance of early diagnosis and intervention (Table 1).

Case 1: A 5-y-old boy of Arabic origin, born uneventfully at full term presented at 2 wk of age with severe dehydration and persistent diarrhea since birth. His admission was complicated with severe metabolic acidosis and seizures due to deranged electrolytes and needed mechanical ventilation. Infective pathology was ruled out and USS abdomen was normal. He had prolonged hospital stay as his diarrhea persisted inspite of hydrolyzed formula. An endoscopic biopsy was carried out at 7 wk of age which was normal. Total Parenteral Nutrition (TPN) was commenced and at 9 mo of age gene panel for CDD's was carried out which revealed a homozygous mutation in *PCSK1 gene (c.1312C > T p.Arg438*).*

At four years he started to show increase in body mass index (BMI), became obese and was investigated for endocrine abnormalities. A water deprivation test confirmed partial DI and GH deficiency and he was commenced on Desmopressin and GH injections.

Case 2: A younger sibling of Case 1 presented at 2 wk of age with severe watery diarrhea. Genetic studies revealed the same homozygous mutation in *PCSK1 gene(c.1312C > T p.Arg438*)* as his elder brother. By the age of two years, he became obese and was screened for endocrine abnormalities and found to have partial DI, hence was commenced on Desmopressin.

PC1/3 is an essential enzyme which is imperative for activation of biologically inactive hormones [3]. Affected children present in the neonatal period with severe diarrhea, but are frequently misdiagnosed given the rarity of the disorder. Unlike other CDD's, the diarrhea in children with PC1/3 deficiency improves over time. The patients gradually start to have solid stools, may become TPN independent and generally become obese [4]. If the children survive the infantile period, they develop endocrinopathies in the "second phase" of the disorder due to impact of PC1/3 on processing prohormones, leading to DI like disorder, GH deficiency, hypogonadism, hypoadrenalism *etc.* [5].

Despite being a rare diagnosis, pediatricians should be aware of PC1/3 especially if a neonate presents with severe, profuse diarrhea of unknown origin. As highlighted in our cases, early diagnosis may not prevent obesity, but may aid

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Table 1 Summary of clinical features of two siblings with *PCSK1* mutation

	Case 1	Case 2
Ethnicity	Arabic	Arabic
Sex	Male	Male
Outcome;Age	Alive; 5 y	Alive; 3 y
Consanguinity	Yes	Yes
Family history	No	No
Birth Weight	3.5 kg	2.97 kg
Age presented	2 wk	2 wk
GI manifestations	Yes	Yes
Age of onset of obesity	4 y	2 y
Onset of Diabetes Insipidus	2 y	19 mo
Growth hormone deficiency confirmed; Age; Treated	Yes; 4 y; on growth hormone therapy	No
Hypothyroid	No	No
Hypogonadism	No	No
Hypocortisolism	No	No
Post prandial hypoglycemia	No	No
Current weight/ percentile	32 kg (on 98th percentile)	17 kg (on 97th percentile)
Current height/percentile	113 cm (on 20th percentile)	93 cm (on 40th percentile)
BMI	25.06 kg/m^2	25 kg/m^2
Current medications	Growth hormone, Desmopressin	Desmopressin

BMI Body mass index

in early diagnosis of endocrine abnormalities which may improve quality of life and reduced hospital admissions.

Compliance with Ethical Standards

Conflict of Interest None.

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