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CASE REPORT

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Protein-losing enteropathy with congenital kidney stones in a 2-month-old boy: a rare case report and literature review

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Abstract

Background Protein-losing enteropathy (PLE) is a rare condition featured by severe loss of proteins through the gastrointestinal tract. Rare PLE cases complicated with congenital kidney stones have been reported. This case study aimed to illustrate our experiences on the diagnosis and treatment of PLE and congenital kidney stones in a neonate.

Case presentation A 10-day-old boy fed on breast milk presented to our department because of severe diarrhea, which showed no significant attenuation after free amino acid milk formula. Gastrointestinal endoscopy revealed absence of brush border of surface villi. Genetic testing was strongly recommended given intractable early-onset diarrhea, severe malnutrition and hypoalbuminemia. Then the patient was diagnosed with PLE based on the clinical manifestations and identification of *DGAT1* gene by whole-exome sequencing. The patient underwent percutaneous suprapubic cystostomy to remove the urine, and ultrasonography examination showed kidney stones.

Conclusions We reported a rare newborn with PLE and congenital kidney stones carrying *DGAT1* mutations.

Keywords Protein-losing enteropathy, *DGAT1* deficiency, Kidney stones, Case report

Introduction

Protein-losing enteropathy (PLE) is a rare condition featured by excessive protein loss from the gastrointestinal (GI) tract [1]. Three main groups of disorders have been reported to be associated with its etiology, including primary erosive/ulcerative, non-erosive/non-ulcerative GI disorders, and disorders causing increased lymphatic/interstitial pressure [2]. For the pathophysiology, this condition results from the destruction of the intestinal mucosal barrier or failure of lymphatic drainage, leading to excessive leakage of serum proteins into the gut, and poor reabsorption [3]. Therefore, patients with PLE usually present with fat-soluble vitamin deficiencies, fat malabsorption, hypoproteinemia, as well as malnutrition.

A subset of PLE presents in early infancy, characterized by early-onset chronic diarrhea. These cases are part of the broader category of congenital diarrheas and enteropathies (CODEs), which are commonly associated with feeding intolerance and malabsorption [4, 5]. It has been well acknowledged that *DGAT1* mutations have been reported to involve in the pathogenesis of PLE and/or CODEs [6, 7]. Actually, great advances have been made in underlying the genetic basis of these disorders with

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the availability and progress next-generation sequencing (NGS).

Kidney stones, a common entity in adulthood, is rare in newborns [8]. To our best knowledge, no case with concurrent PLE and kidney stones has been reported after a comprehensive literature research. Here, we reported our experiences on the diagnosis of a rare case of PLE and congenital kidney stones with *DGAT1* mutation based on whole-exome sequencing (WES).

Case presentation

A 10-day-old boy fed on breast milk presented to our hospital due to severe diarrhea with a frequency of >10 times per day, concurrent with intermittent vomiting. He was born vaginally at a gestational age of 38 weeks, with a birth weight of 2.6 kg. Initially, the patient was suspected with feeding intolerance. Upon admission, the feeding regimen was switched to free amino acid milk powder, and then the frequency of diarrhea was reduced to about 2–3 times per day and the patient was discharged. Unfortunately, the frequency of diarrhea escalated again to 5 or 6 times per day two months later. The diarrhea was slightly relieved after switching to extensively hydrolyzed formula (medium chain triglyceride content 50%, and lactose free). Subsequently, the patient showed loose stools containing a small amount of mucus with a frequency of 4 times per day with intermittent vomiting.

Gastrointestinal endoscopy revealed increased infiltration of inflammatory cells in the duodenal mucosa, and the brush border of surface villi was no longer available (Fig. 1). Given intractable early-onset diarrhea, severe malnutrition and hypoalbuminemia, genetic testing was strongly recommended. After obtaining the written consents from his parents, WES was performed after collecting peripheral blood from the child, and parents' peripheral blood was collected for Sanger sequencing. Sanger sequencing results confirmed the presence of heterozygous variants in *DGAT19* (NM_012079.5) gene (i.e. c.276T>A and c.214 C>T), which was a paternally inherited mutation at chr8: 145,544,996, and a maternally inherited mutation at chr8: 145,545,058, respectively (Fig. 2). Based on this, the patient was diagnosed with PLE caused by an autosomal recessive variant in the *DGAT1* gene.

When the patient was 10 days old, kidney ultrasonography showed multiple renal calculi (Fig. 3A and B). Therefore, we suspected that the kidney stones were congenital. The boy presented to our department again at the age of 1 year and 4 months since he had no urination combined with scrotal edema for 2 days. Emergency ultrasonography and CT scan examination showed multiple kidney stones (Fig. 3C and D). Later, the patient was urgently admitted to PICU due to sepsis caused by acute urinary retention and urinary tract infection, infectious fever, electrolyte imbalance, abnormal coagulation function, kidney stones, bilateral hydronephrosis, ureteral dilatation. In the PICU, the patient received hood oxygen therapy, plasma transfusion, anti-infection treatment (meropenem 20 mg/kg) and anti-inflammatory treatment (methylprednisolone sodium succinate 1 mg/kg).

The patient underwent percutaneous suprapubic cystostomy to remove the urine before being transferred to our hospital. There was no vomiting of blood, blood in the stool, or epistaxis during hospitalization. After onset, the infant did not vomit with regular extensively hydrolyzed formula (medium chain triglyceride content 50%) intake and had poor milk feeding. There was no peripheral cyanosis in complexion and lips.

In the follow-up, his body weight was 5 kg, and his height was 62 cm at the age of 1 year and 7 months old. Now, the patient still shows diarrhea with a frequency of 4–6 times per day. His weight gain is not in the normal range, and he still requires fistula caring. He is feeding with hydrolyzed medium chain triglyceride milk together with a regular diet.

Discussion

In this study, we reported our experiences on the diagnosis and treatment of a rare case of PLE and congenital kidney stones in a male neonate. Because of the rarity of

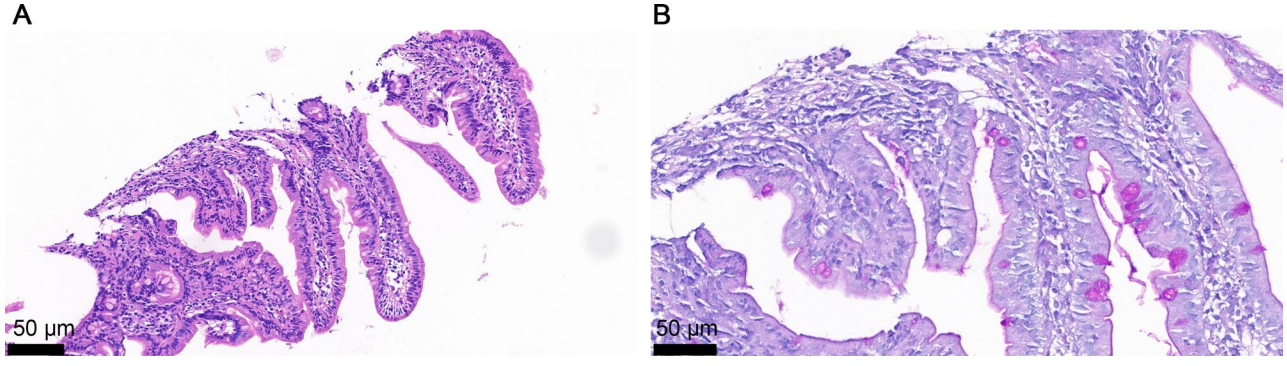

Fig. 1 Pathological staining results. (**A**) Histopathology of a duodenal biopsy from the patient showed that duodenal villous brush border disappeared. (**B**) The PAS staining demonstrated heavy inflammatory infiltrate in duodenal mucosa

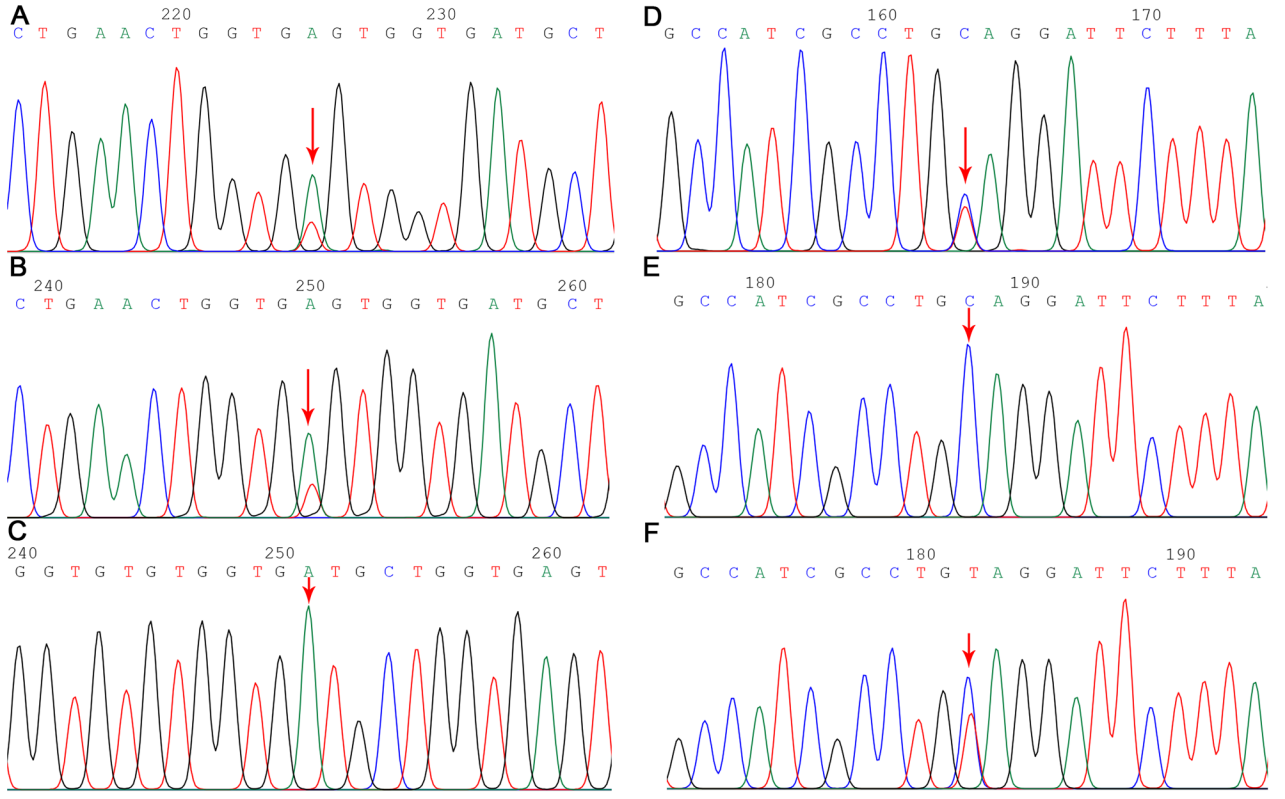

Fig. 2 Sanger sequencing results showed mutations in *DGAT1* detected in the patient's family. (**A**) Chromatogram showing the patient with a heterozygous mutation at chr8:145544996, c.276T > A. (**B**) Chromatogram showing the patient's father carrying the same heterozygous mutation, c.276T > A. (**C**) Chromatogram showing the patient's mother with no mutation at this site. (**D**) Chromatogram showing the patient with another heterozygous mutation at chr8: 145,545,058 c.214 C > T. (**E**) Chromatogram showing the patient's father with no mutation at this site. (**F**) Chromatogram showing the patient's mother carrying the same heterozygous mutation c.214 C > T

PLE, the diagnosis of PLE was not initially considered. According to our experiences, the patient was initially diagnosed with diarrhea in infants, hypoalbuminemia, hyperbile academia, and gastroesophageal. However, after a long-term alternative to the free amino acid milk, the conditions showed no improvement, and then WES was conducted for further diagnosis. To our best knowledge, this is the first case of *DGAT1* mutations with PLE and kidney stones.

DGAT1 gene is ubiquitously expressed in the human intestine, which encodes DGAT1 protein catalyzing the final step in cellular synthesis of triglyceride (TG) [9]. A previous study [10] revealed that mutations in *DGAT1* could down-regulate the expression of DGAT1 protein and trigger alternation of triacylglycerol metabolism in patient-derived fibroblasts and organoids. Haas et al. showed a case of PLE and early-onset diarrhea carrying *DGAT1* mutations [7]. Generally, excessive generation of diacylglycerols or fatty acids may be toxic by acting as bioactive signaling lipids, or by detergent-like behaviors of fatty acid moieties, which may be closely related to the pathogenesis of PLE. Van et al. found that *DGAT1*-deficient organoids were more susceptible to lipid-induced toxicity, which may reflect the clinical features of PLE patients with *DGAT1*-deficiency [10]. To date, several mutations in *DGAT1* have been commonly described in patients of Ashkenazi Jewish, Turkish, Caucasian and Chinese. Patients with *DGAT1* deficiency have largely presented within the first few months of life, which are featured by early-onset, non-bloody watery diarrhea, vomiting, persistent hypoalbuminemia, and failure to thrive [11]. Recent studies revealed that some patients had delayed-onset chronic diarrhea beyond the neonatal period, which may be related to their heterozygous mutations in *DGAT1* [11]. For these patients, the treatment mainly relies on limiting enteral fat intake in conjunction with intravenous lipid administration [6]. In our case, the heterozygous *DGAT1* loss of function was associated with the pathogenesis of PLE, which was supported by the phenotypes.

DGAT1 mutations can cause variant symptoms including lipid malabsorption and dysfunction of multiple organs. A previous study [12] revealed that *DGAT1b* may serve as the target gene of NF-κB p65 which linked LPS signaling and TG synthesis in vertebrates. Recent studies indicated that accumulation of renal lipids played a

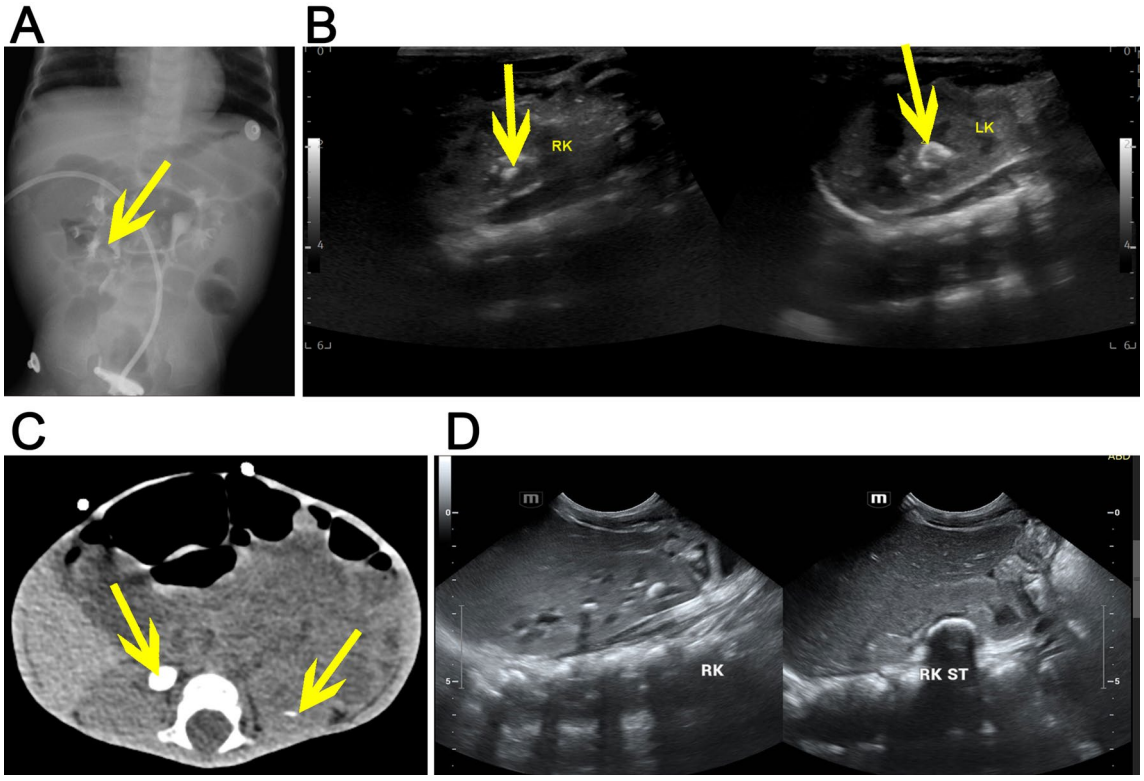

Fig. 3 Imaging findings of the patient. (**A**) Intravenous pyelography showing right renal pelvic filling defect, suggesting renal pelvic calculi. (**B**) Renal ultrasound showed kidney stone in the left kidney and right kidney. (**C**) CT scan showed renal calculi. (**D**) Renal ultrasound showed multiple renal calculi in the right kidney with acoustic shadowing and larger stones in the right kidney with acoustic shadow

crucial role in the progression of renal diseases, including chronic glomerulopathy, chronic renal insufficiency, obesity-associated renal disease, as well as acute kidney injury [13]. In contrast with previous studies, our patient had congenital kidney stones combined with PLE. This may be associated with the fact that continuous compensation of electrolytes through the kidney may cause kidney injury [14]. Many pediatric patients with intestinal failure showed increased echogenicity and nephrocalcinosis that was associated with prolonged parenteral nutrition exposure [15]. Recent studies showed chronic dehydration could negatively affect renal function [16, 17]. As an alternative, bile acid malabsorption affected by *DGAT1* deficiency may lead to diarrhea. In addition, the studies by Zhao et al. [18]. and Wang et al. [19]. revealed a close link between abnormal lipid metabolism and kidney stone formation. In this report, the *DGAT1* gene mutations may lead to lipid metabolism disorders, which could be a potential mechanism for the formation of congenital kidney stone. Our patient also had hyperbilirubinemia, provided available information on fecal bile acid levels in the affected individuals.

Indeed, early diagnosis and treatment are crucial for diarrhea in neonates, as it may rapidly lead to life-threatening dehydration and malnutrition. Here, WES was utilized to identify the mutation in the *DAGT1*. Genetic testing identifies the diagnosis underlying PLE in children, and in the future, more studies are required to further illustrate its utility in the neonatal diagnosis.

Conclusions

We reported a rare case of PLE and congenital kidney stones in a neonate. *DGAT1* deficiency should be highly suspected for infants with unexplained diarrhea and vomiting accompanied by PLE. WES may be used as an effective method for the early genetic detection together with pathological intestinal analysis.

Abbreviations

CODEs	Congenital diarrheas and enteropathies
DGAT1	Diacylglycerol acyltransferase 1
GI	Gastrointestinal
NGS	Next-generation sequencing
PLE	Protein-losing enteropathy
TG	Triglyceride
WES	Whole-exome sequencing

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Not applicable.

Author contributions

Jiahui Fang: Data analysis, Writing - Original Draft. Zhuoheng Li: Data analysis, Writing - Original Draft. Lin Zhang: Data collection, Writing - Review & Editing. Qiaojian Liu: Data collection, Writing - Review & Editing. Jie Mao: Data analysis, Writing - Review & Editing. Jintao Duan: Conceptualization, Funding acquisition, Writing - Review & Editing.

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Data availability
The sequence of DGAT1 is publicly available in NCBI (https://www.ncbi.nlm.nih.gov/nuccore/NM_012079.5/). The VCF file of WES is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed according to the convention of the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of Kunming Children's Hospital. Written informed consent was obtained from the patient's parents.

Consent for publication
Written informed consent to publish this case was obtained from the patient's parents, including case description and medical data.

Competing interests
The authors declare no competing interests.

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