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Case Report

Novel Variant in the Plasmalemma Vesicle-Associated Protein Gene PLVAP Causes a Severe Protein Losing Enteropathy Syndrome

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Abstract

Variants in PLVAP gene caused to date a severe (lethal) syndrome characterized by severe protein-losing enteropathy (PLE) with congenital hypothyroidism additionally suffer the affected patients from dysmorphic features and congenital diarrhea, otherwise occur the clinical manifestations early in the neonatal period and infancy. Attenuated disease was also mentioned due to the variants in PLVAP characterized by mild PLE without any dysmorphic features, hypothyroidism, or other organ abnormalities.

To date, five cases of this syndrome have been described. Herein, we report a newborn who developed secretory diarrhea metabolic acidosis, anasarca, sepsis, respiratory and heart failure during the first week of age. Furthermore, the patient had congenital hypothyroidism and dysmorphic facial features. Whole-exome-sequencing (WES) revealed a non-described homozygous pathogenic out-of-frame-deletion c.670-676del in the PLVAP gene causing a premature stop codon p.(Leu224Cysfs*54).

In agreement with previously published reports our recommendation is to screen all infants with protein-losing enteropathy, congenital hypothyroidism and facial dysmorphism for PLVAP variants.

Keywords: *Protein-Losing Enteropathy (PLE); Whole-Exome-Sequencing (WES); Plasmalemma Vesicle-Associated Protein Gene PLVAP*

Introduction

Protein-losing enteropathy (PLE) is characterized by excessive loss of protein often due to the disruption of the integrity of the intestinal mucosal membrane or dilatation of the intestinal lymphatic system. Two broad categories of PLE have been described: mucosal injury causing the excessive losses observed in inflammatory bowel disease (IBD) and intestinal infections, and abnormalities of the lymphatic system observed in primary intestinal lymphangiectasia [1,2].

A crucial role for PLVAP in the regulation of vascular permeability has been detected [3,4]. PLVAP variants leading to deletion of the diaphragms of endothelial fenestrae, resulting in plasma protein extravasation. The total loss of function of PLVAP strongly cause severe protein losing enteropathy (PLE) and syndromic features. The clinical hallmarks of PLVAP-associated (lethal) PLE syndrome are facial dysmorphic features (long philtrum, wide, depressed nasal bridge, low set ears), congenital hypothyroidism, renal abnormalities, intractable secretory diarrhea with severe hypoalbuminemia and electrolyte abnormalities.

Elkadri., *et al*. initially mentioned the association between a nonsense variant in the PLVAP gene and the cause of PLE syndrome [5]. Subsequently, Broekaert., *et al*. described a different nonsense PLVAP variant in another patient with a similar clinical picture [6]. These two patients had PLE, hypothyroidism diarrhea, edema, hypoalbuminemia, dysmorphism, venous thrombosis, electrolyte distributions, renal and iris abnormalities.

Case Report

A full-term male was born at 37 + 5 by spontaneous vaginal delivery in our hospital. was the first child to healthy consanguineous parents (first cousins) from Afghanistan.

Pregnancy was unremarkable. Family History negative. He was born with normal umbilical cord-ph no neonatal asphyxia. Birth weight was 1.93 kg (1 p), a length of 39.0 cm (1 p), and a head circumference of 33.0 cm (5-10 p). Apgar's score was 06/09/10. Vital signs were normal.

Due to the low birth weight (SGA) and dysmorphic characteristics (Figure 1), the newborn was admitted to our NICU. The systemic examination was normal.

Figure 1: *Shows the dysmorphic features: thin upper lip, long philtrum, broad nasal bridge, prominent maxillae, low-set ears, and eyelid edema.*

A newborn screening that included thyroid-stimulating hormone TSH was unremarkable, and two controls of complete blood count, C-reactive protein levels, Interleukin 6 levels, liver parameters, random, fasting blood glucose measurements and blood gas analyses with electrolytes revealed no abnormalities.

Thyroid sonography demonstrated a normally sized non-ectopic thyroid gland. but has echogenic tissue. The renal USG identified otherwise normally sized echogenic kidneys.

The results of the echocardiography, liver and cranial ultrasound exams were all normal.

The second day of life the newborn was stable and showed well breastfeeding; as a result, he was transferred to our medical care unit with his mother. He was readmitted to the NICU due to secretory diarrhea, tachypnea, dyspnea, and dehydration on the fifth day of life.

The laboratory result revealed a severe mixed respiratory and metabolic acidosis with normal lactate. Hyperglycemia (255 mg/dl) was noted.

Additionally, leukocytosis (28,000/µl), thrombocytopenia (50,000/µl) were present along with hyponatremia (Na 121 mmol/l), hypocalcemia (tca 1,5 mmol/l), and hypomagnesemia (Mg 0,62 mmol/l), low blood urea nitrogen (BUN) and a high creatinine level (0.9 mg/dl). Despite unremarkable crp (0.6 mg/l) and IL6 (102 pg/ml) multi-sensible *Streptococcus vestibularis* was detected in the blood culture.

Both viral PCR detection and bacterial growth were absent from stool culture. The urine assay was normal, no proteinuria.

Although the free thyroxine Ft4 was undetectable with a normal thyroid-stimulating hormone TSH value, he had severe hypoproteinemia and hypoalbuminemia (1,1 g/dl and 0,4 g/dl, respectively), massively low serum amino acid concentrations, notably the essential amino acids, and abnormally Quick and protracted aptt. Moderate hypertriglyceridemia (282 mg/dl) was observed.

The acylcarnitine profile, fat oxidation function, ammonia levels, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphatase (AP), and lactate dehydrogenase (LDH), as well as the organic acid in urine and serum, were all within normal value. Immunoglobulin levels and fecal a1-antitrypsin were not assessed.

A large thrombus at the tricuspid valve, a minimal pericardial effusion and a massively reduced right ventricle function detected by echocardiography (Figure 2). Retrospectively, endocarditis and pulmonary embolism were considered as a differential diagnosis.

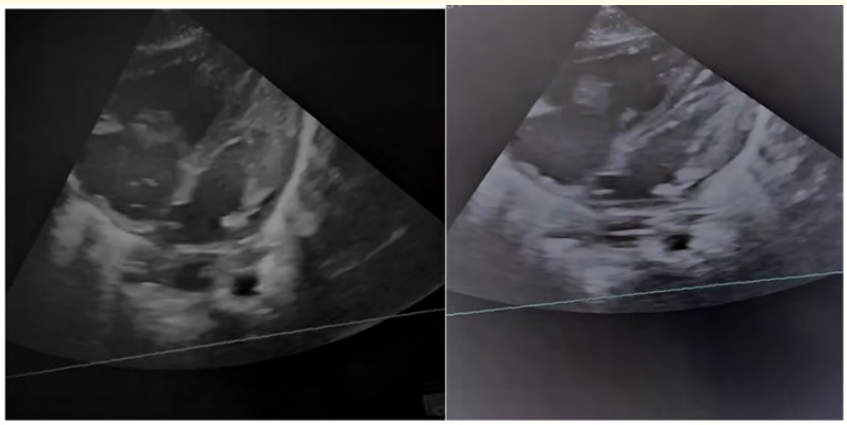

Figure 2: *Echocardiography four chamber view shows large thrombus at the tricuspid valve.*

Ultrasound of the abdomen revealed an enlarged liver, ascites, dilated and swollen small intestinal loops, no peristalsis, and no pneumatosis. A chest x-ray was normal.

After non-invasive respiratory support therapy, intubation and mechanical ventilation with pressure controller-assistant control (PC-AC) were used due to the patient's rapid respiratory deterioration.

Other than treating the hypocalcemia, hyponatremia, hypomagnesemia, and hypothyroidism (intravenous liothyronine), we started with a broad-spectrum antibiotics meropenem plus vancomycin and transfused platelet concentrates.

In addition to the aforementioned metabolic acidosis, the patient also rapidly developed ascites, anuria, refractory hypotension, and generalized edema. No improvement in blood pressure or metabolic acidosis was seen despite resuscitation with fluid, sodium

bicarbonate, albumin, Fresh Frozen Plasma (FFP), blood transfusion, hydrocortisone, continuous infusion of milrinone, inhaled nitric oxide therapy, and catecholamines (epinephrine, norepinephrine, dobutamine, dopamine, and vasopressin, respectively).

There was no examination by the ophthalmologist.

Due to sepsis (or endocarditis), Disseminated intravascular coagulation (DIC) and right heart failure, the newborn sadly passed away on the eighth day of life despite the maximum therapy.

Analysis of exome-based NGS-sequencing data (Human Core Exome Enrichment Kit; Twist Bioscience) revealed homozygozity for out-of-frame deletion NM_031310.3 (PLVAP): c.670_676del p.(Leu224Cysfs*54) causing a premature stop codon. Subsequent analysis of his parents will be update later.

Discussion and Conclusion

It was shown that PLVAP knockout mice survived postnatally up to 4 weeks or survived up to 3 - 4 months, respectively, but suffered from growth retardation, anemia, and selective leakage of plasma proteins into the interstitium with subsequent edema and dyslipidemia, eventually leading to a lethal, protein-losing enteropathy [4,7,8].

Moreover, humans that own a nonsense variants in the PLVAP-gene develop similar disease profiles characterized by protein losing enteropathy, hypoproteinemia, hypoalbuminemia, and hypertriglyceridemia, which can lead to a severe PLE syndrome and death [5].

Here, we present the sixth patient who has a congenital lethal PLE syndrome caused by a novel homozygous variant in the PLVAP gene. He suffered from secretory diarrhea, metabolic acidosis, congenital hypothyroidism, severe anasarca, tricuspid valve thrombosis, and significant hypoalbuminemia, Similar to other cases that have been previously mentioned.

Elkhadri A., *et al*. described the first patient with homozygous nonsense variant in the PLVAP gene in 2015 presented at 8 days of life with nearly similar symptoms as our patient. He developed later nosocomial infection with multiorgan failure and death at 136 days.

The second patient was found to have a new homozygous nonsense variant in the PLVAP gene that caused severe PLE and syndromic characteristics, according to Broekaert., *et al*. The boy experienced haematochezia and died on the fifteenth day of his life, most likely as a result of DIC.

Kurolap., *et al*. detected a missense variant in the PLVAP gene in two different individuals with consanguinity. The patients presented with a similar, although milder and with later onset age (2,5 and 22 year), phenotype of PLE and partial penetrance of hypertriglyceridaemia without dysmorphic feature, which are managed with a low-fat diet and a middle-chain triglyceride-rich formula with significant clinical and laboratory improvement, allowing them to resume normal lives [9]. The later onset of symptoms in the patients could be attributed to the missense nature of the pathogenic variant (p.Leu34Pro), compatible with residual PLVAP function.

Finally, O. Gorukmez., *et al*. [10] found a homozygous frameshift variant resulting in premature stop codon in exon 1 of the PLVAP gene. This was detected in 2,5 months female which died at 22 months of age due to severe lung infection. the clinical, biochemical and radiological features were similar to these patients described by Elkadri., *et al*. and Broekaert., *et al*.

In conclusion, four patients from the mentioned cases died; all of them had dysmorphic features, severe PLE (hypoproteinemia, hypoalbuminemia, hypertriglyceridemia, anasarca), hypothyroidia, severe infection, and thrombosis. The another two patients developed mild PLE without dysmorphic features, hypothyroidia or other organ abnormalities.

We can initially categorize this syndrome probably after carefully reviewing the entire cases to date in two forms:

1. Lethal congenital PLE syndrome with hypothyroidism.
2. Mild congenital PLE without hypothyroidism.

Support for this classification is possible with more research and record more cases.

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Conflicts of Interest

The authors disclose no conflicts.

Disclosure Statement

The authors have no financial relationships relevant to this article to disclose.

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