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Primary Intestinal Lymphangiectasia presenting as limb Convulsions : a case report

Yun Cao, Xiao-Hong Feng, Hai-Xiang Ni

Abstract

BACKGROUND

Primary intestinal lymphangiectasia (PIL) is a rare protein-losing enteropathy characterized by abnormally dilated lymphatic structures resulting in leakage of lymph (rich in protein, lymphocytes, and fat) from intestinal mucosa and submucosa layers resulting in hypoproteinemia, lymphopenia, lower lipidemia as well as pleural effusion.

CASE SUMMARY

A 19-year-old Chinese male patient complained of recurrent limb convulsions for the last one year. Laboratory investigations revealed low levels of calcium and magnesium along with hypoproteinemia and high parathyroid hormone (PTH) levels, whereas gastroscopy exhibited chronic non-atrophic gastritis and duodenal lymphatic dilatation. Subsequent gastric biopsy showed a moderate chronic inflammatory cell infiltration distributed around a small mucosal patch in the descending duodenum followed by lymphatic dilatation at mucosal lamina propria, which was later diagnosed as PIL followed by appropriate medium-chain triglycerides (MCT) nutritional support that significantly improved the patient's symptoms.

CONCLUSION

Since several diseases mimic the clinical symptoms displayed by PIL, like limb convulsions, low calcium, and magnesium along with loss of plasma proteins, it is imperative to conduct a detailed analysis for avoiding any misdiagnosis while pinpointing the correct clinical diagnosis while simultaneously ruling out other clinical aspects in the reported cases without any past disease history. A careful assessment should always be made to ensure an accurate diagnosis in a timely manner so that the patient can be delivered quality health services for a positive health outcome.

Key Words: Protein-losing enteropathy ; Primary intestinal lymphangiectasia ; limb convulsions ; adult ; case report

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Core Tip: In our case, we found A 19-year-old Chinese male patient complained of recurrent limb convulsions for one year. Laboratory investigations revealed low levels of calcium and magnesium along with hypoproteinemia and high PTH levels, but the patient had no limbs edema which is rear in PIL case.Differential diagnosis is the difficulty of the whole case. Careful analysis and examination results finally enabled the patient to receive effective treatment after definite diagnosis.

INTRODUCTION

Intestinal lymphangiectasia (IL) is a rare protein-losing enteropathy[1], characterized by small intestine lymphatic drainage obstruction, chylous ascites, and villi distortion that further cause lymphatic congestion and elevate the lymphatic pressure, thereby resulting in leakage of lymph liquid into the small intestine lumen. IL can be categorized into two forms, primary intestinal lymphangiectasia (PIL) and secondary intestinal lymphangiectasia (SIL). PIL, first reported by Milroy in 1892, is more common in children and adolescents, though rarely, it can also occur in adults and has a tendency to occur sporadically with an unknown etiology. Waldmann [2] in 1961 after demonstrating protein loss quantification by ^{51}Cr-labelled albumin revealed that the lymphatic vessels present in the mucosal and submucosal layer of the small intestine were abnormally dilated to varying degrees. Hence, this diagnosis came into existence.

The incidence of PIL is likely to be related to lymphatic dysplasia in infants which is more frequently diagnosed in children（less than 3 years old）, but also in adolescents and even elderly cases [3]. Although in most cases lymphatic dilation is typically seen in the descending duodenum, lymphatic dilation in the small intestine is usually mild and segmental, and secondary causes should be excluded. In this case report, a 19-year-old adult male complained of limb convulsions for the past one year, which after further investigations, was later identified as PIL followed by MCT nutritional support that improved the patient's condition.

CASE PRESENTATION

Chief complaints

A 19 years old Chinese male patient complained of recurrent limb convulsions for the past one year.

History of present illness

The patient experienced recurrent limb convulsions and numbness with an unknown medical history in the absence of any aggravating factors like joint inflammation,

edema, headache, dizziness, nausea and vomiting, abdominal distention, pain, or diarrhea leading to a gradual weight loss by five kg but due to ignorance of the patient as well as his family, no further treatment was initiated. But a week ago, his symptoms, comprising of limb convulsions and numbness, got so aggravated that he reported to the community hospital in April 2021 for a thorough examination that was preceded by laboratory investigations that showed reduced levels of blood calcium 1.50 mmol/L(1.95mmol/L after correction, normal range: 2.08-2.6mmol/L), magnesium 0.49 mmol/L (normal range:0.75-1.02mmol/L), potassium 3.38 mmol/L (normal range:3.5-5.5mmol/L), and albumin 17.27 g/L(normal range:40-55g/L) while displaying increased parathyroid hormone (PTH) 113.0 pg/mL(normal range:15-65pg/mL), followed by blood phosphorus 1.12 mmol/L, TSH 2.5 mIU/L and a positive fecal occult blood test (FOBT) after which the patient was supplemented with albumin, calcium gluconate injections as well as potassium magnesium aspartate. Henceforth, the persistent symptoms like limb convulsions and numbness were relieved after symptomatic treatment for one week. He went to the Endocrinology department of our hospital for a further definite diagnosis.

History of past illness
The patient was healthy until the age of 18, with no trauma or any history of the tumor.

Personal and family history
The patient was born by spontaneous labor at term, was breastfed in infancy, had normal physical and cognitive development as his peers along with good academic performance. However, he had a history of hemorrhoids but did not have any long-term chronic abdominal pain and diarrhea in adolescence.His parents were healthy while denying any history of familial genetic disease, psychosis, and infection in the older family generations.

Physical examination

Height 174cm, weight 52kg, BMI 17.18kg/㎡, The patient did not exhibit widening of either eye distance or base of the nose-bridge and small external ear while his abdomen was flat and soft, with no abdominal tenderness and rebound pain, non-palpable liver and spleen, normal bowel sounds, and limb strength. Especially no concave edema was found in both lower limbs, whereas the Babinski sign, facial nerve percussion sign, and bundle arm compression sign were negative.

Laboratory examinations

Blood calcium 2.37mmol/L (normal range: 2.08-2.6mmol/L), blood magnesium 0.73mmol/L (normal range: 0.75-1.02mmol/L,), blood potassium 4.19mmol/L, blood phosphorus 1.19mmol/L, parathyroid hormone 16.7pg/mL (normal range: 15-65pg/mL), albumin 25.2g/L↓ (normal range: 40-55g/L), FOBT 1+

Blood routine: WBC 3.8*109 /L, lymphocyte count 0.41*109 /L (normal range:1.1-3.2*109 /L), lymphatic percentage 10.4% (normal range: 20-50%)

Fat-soluble vitamins: vitamin A 0.28ug/mL(normal range:0.30-0.70ug/mL), 25 hydroxyvitamin D 5.28ng/mL(<20ng/mL deficiency), vitamin E 4.49ug/mL (normal range : 0.30-0.70ug/mL) vitamin K1 0.12ng/mL (normal range : 0.20-2.50ng/mL)

Immunoglobulin A 0.49g/L(normal range : 0.82-4.53g/L), immunoglobulin G 1.44g/L(normal range : 7.51-15.6g/L), immunoglobulin M 0.18g/L(normal range: 0.46-3.04g/L), complement C3 0.67g/L↓ (normal range: 0.79-1.52g/L), complement C4 0.15g/L↓ (normal range: 0.16-0.38g/L);Transferrin 1.42g/L(normal range: 2.0-3.6g/L); The copper orchid protein 10.70mg/ dL (normal range: 22-58mg/ dL);

T cell subpopulation: B cells (CD19+) 38*106 /L↓ (normal range: 50-670*106 /L), T cell number (CD3+CD45+) 179*106 /L(normal range: 470-3270*106 /L), T helper number (CD3+CD4+) 46*106 /L(normal range: 200-1820*106 /L), T inhibitory number (CD3+CD8+) 120*106 /L(normal range:130-1350*106 /L), the number of NK cells was normal.

HIV+RPR: negative, blood IBD, stool IBD screening showed no obvious abnormalities.

Normal liver and kidney function, normal thyroid function, thyroglobulin, thyroglobulin antibody, thyroid peroxidase antibody were normal range;

ACTH: 8AM 13.2ng/L, 4pm 12.6ng/L, 0AM 5.3ng/L;

Cortisol: 8am 174.3nmol/L, 4pm 102.7nmol/L, 0AM <25nmol/L;

Sex hormones: follicle stimulating hormone 5.98IU/L, luteinizing hormone 7.74IU/L, estradiol 98.38pmol/L, testosterone 27.56nmol/L;

Growth hormone: insulin-like growth factor-1 208ug/L, insulin-like growth factor binding protein-3 4.8mg/L;

Tumor, ANA spectrum, ANCA, rheumatoid factor, ESR and hepatic fibrosis were all in the normal range.Urine immunoglobulin light chain, 24h urine protein, 24h urine calcium within the normal range.

Imaging examinations

B-mode ultrasound imaging of the parathyroid gland revealed a hypo-echoic nodule with a clear boundary and a regular shape along with few blood vessels（Fig2）, whereas an MRI examination exhibited no obvious abnormality while an abnormal-signal nodule was found in front of the right middle abdominal psoas muscle, which was considered as an enlarged lymph node followed by a scanty exudate at the abdominal and pelvic cavity, along with cortical soft tissue edema. Capsule endoscopy showed the flat composition of duodenal mucosa villi with no obvious abnormality in jejunal or ileal mucosa.gastroscopy exhibited chronic non-atrophic gastritis and duodenal lymphatic dilatation（Fig3）. Subsequent gastric biopsy showed a moderate chronic inflammatory cell infiltration distributed around a small mucosal patch in the descending duodenum followed by lymphatic dilatation at mucosal lamina propria（Fig4）.

FINAL DIAGNOSIS

Finally, He was diagnosed with PIL（Fig3；Fig4）

TREATMENT

The patient was treated with a low-fat, high-protein, light diet which contains 1800 calorie each day, and with MCT powder supplement, calcid calcium supplement, and roquettin vitamin D supplement.

OUTCOME AND FOLLOW-UP

The patient was returned to the clinic 3 mo later, and showed no symptoms of convulsion of limbs. Meanwhile, blood calcium and albumin in the laboratory examination increased compared with before.

DISCUSSION

The clinical manifestations of PIL are diverse as they may cause dilatation of the intestinal lymphatic vessels leading to loss of lymph fluid into the gastrointestinal tract. While it is mainly characterized by edema of varying degrees, it can also be manifested as pleural effusion, pericarditis, chylous ascites, diarrhea, fat vitamin deficiency, weight loss, and other symptoms occurring in severe cases. In our case, due to unknown past medical history, diagnosing and providing prompt treatment was initially challenging as there was no clear history of diarrhea and abdominal pain, limb convulsions, and disease symptoms in childhood. The now obvious limb convulsions first appeared when the patient was 18 years of age and manifested themselves as hypocalcemia, hypomagneemia, hypoproteinemia levels along with elevated PTH levels. Due to similar propensity and characteristics, this disease can easily mimic Pseudohypoparathyroidism (PHP) disease and some other similar diseases in internal medicine, which might lead to misdiagnosis leading to a plethora of unpleasant side effects. Therefore, the foremost thing that is recommended is to reach a definite diagnosis for a positive outcome.

Laboratory tests at presentation suggested hypocalcemia, hypomagneemia, hypoproteinemia, and lymphocytopenia. Further investigation revealed elevated PTH, decreased Vitamin D, low immunoglobulinemia, and positive FOBT. First, the patient

had hypocalcemia and hypomagnesemia, and the convulsions of the limbs were relieved by calcium gluconate and potassium magnesium aspartate. Elevated PTH and hypoproteinemia gave us the impression of renal insufficiency, but subsequent negative results of renal function and urinary protein preclude this diagnosis. Laboratory tests revealed normal liver function and negative rheumatoid and tumor markers, so we focused on the parathyroid gland. According to B-ultrasonography, hyperplasia of nodules, elevated PTH and hypocalcemia were suggested, which was first considered as diseases of endocrinology.

PHP is a genetic disease in which peripheral cells are resistant to PTH [4]. The central link of the disease is PTH resistance, which leads to high blood phosphorus and activation disorders of 25-(OH)D3, eventually leading to hypocalcaemia. Although this disease is common in women but more severe in men, the reported patients showed symptoms at two years of age which became more obvious after the age of ten but can rarely be seen in people aged 20 years or above. Tetany and intracranial calcification are usually the most common clinical manifestations and imaging features of PHP. PHP patients with vitamin D deficiency have more severe clinical symptoms, and vitamin D deficiency increases the risk of autoimmune disease. Vitamin D is mainly synthesized in the skin of the body, and then converted into 25-(OH)D by the hydroxylation of 25-hydroxylase (CYP27A1) in the liver, which is the main form of vitamin D in the circulation. 25-(OH)D binds to vitamin D binding protein into the blood circulation and generates active metabolite 1,25-(OH)2D under the catalysis of renal 1α -hydroxylase (CYP27B1). 1,25-(OH)2D acts on the intestine, kidney and bone to regulate the metabolism of calcium and phosphorus. In the small intestine, 1,25-(OH)2D promotes the absorption of calcium and phosphorus, and the serum 25-(OH)D is inversely proportional to PTH. When the serum 25-(OH)D level decreases, blood calcium decreases and PTH increases. The increased PTH stimulated the activity of 1α -hydroxylase and increased the efficiency of 25-(OH)D conversion to 1,25-(OH)2D. In addition, PTH also normalizes blood calcium levels by stimulating osteoclast proliferation, increasing bone absorption and calcium release. In this case, the patient

was low in calcium, with compensatory increase of PTH, and the blood phosphorus level was within the normal range during the onset. The reexamination of PTH returned to normal during the further correction of low calcium proved that it was a secondary factor, so PHP could be excluded. Parathyroid nodules were also considered nonfunctional.

Considering the possibility of protein-loss enteropathy, subsequent gastroscopy revealed duodenal lymphatic dilation, confirming our assessment. IL could be divided into primary and secondary types. Primary IL is a congenital lesion with an ambiguous incidence rate and disease mechanism though occurring more sporadically despite the involvement of genetic factors in the pathogenesis,[5] whereas Secondary IL can be caused by several factors as autoimmune diseases (i.e.,Crohn's disease[6], Ulcerative colitis[7], Henoch-Schonlein purpura), tumors (such as non-Hodgkin's lymphoma[8]), infections (such as rotavirus), portal hypertension, constrictive pericarditis[9], trauma or surgical injury[10]. In our case report, Crohn's disease was first excluded as FOBT results showed 1+ repeatedly while blood and stool IBD screening was negative. As he had a previous history of hemorrhoids, the anorectal department considered it as hemorrhoid bleeding after the consultation.

Some PIL patients are found with abnormal immune system responses in which the decrease of B cells is manifested by the decreasing IgG, IgA, and IgM levels[11]. Some previous studies also reported that PIL patients' peripheral blood samples contain a very low number of CD4 $^+$ T cells [12] that were significantly lesser than B cells, while the remaining CD4 $^+$ T cells became highly differentiated and sensitized, thereby showing poor proliferation[13]. It was also observed that the patient's T lymphocytes kept on decreasing in varying degrees in this case. Further evidence will be necessary to determine whether T lymphocytes mediate the immune system functions in the intestine, further leading to the occurrence and development of the disease.

Since the PIL etiology is ambiguous and standardized treatment is inadequate, a study by Alfano *et al*[14] revealed that the primary goal of PIL treatment is to reduce protein loss, maintain circulating blood volume and inhibit excessive tissue fluid

production, thereby indicating that pharmacological treatment is the first-line treatment prescribed in the clinic. In the gastrointestinal tract, MCT is decomposed into glycerol and medium-chain fatty acids that are directly absorbed in the portal vein blood flow by small intestinal epithelial cells without going through lymphatic vessels, thus reducing the pressure in lymphatic vessels, lymph leakage as well as protein loss. Incorporating an MCT-rich diet in daily life could significantly improve the symptoms and long-term mortality of PIL patients, although it might not improve the inherent lymphatic abnormalities; thus, the patients might need to take the required medications for a longer period of time.

CONCLUSION

Based on this case, the PIL as a potential diagnosis should be considered even in the absence of any adolescent-illness history for adults with recurrent limb convulsions, low calcium, magnesium, hypoproteinemia as well as high PTH levels. MCT diet, as a dietary supplement, can effectively improve the clinical symptoms of PIL patients while providing pharmacotherapy after the final diagnosis was made by a thorough detailed analysis.

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