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CASE REPORT

A Rare Case with Pulmonary Embolism and Literature Review

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SUMMARY

Background: **Pulmonary embolism is rare in children, and most of them have high-risk factors, such as antiphospholipid syndrome, intravenous catheterization, fracture bed rest, etc. For children with pulmonary embolism without clear inducement, hereditary thrombophilia should be considered. Genetic protein S deficiency (PSD) is a kind of thrombophilia, which is caused by the mutation of PROS 1 gene, resulting in an increased tendency to thrombosis.**

Methods: **The diagnosis of the two cases was made after detecting based on Thrombophilia screening and Sanger sequencing in clinical laboratory.**

Results: **Sanger sequencing found that case 2 and case 1 genotypes were the same, case 1 sister and grandfather carried c.200a>c (p.e67a) mutation, and case 1 aunt and grandmother did not carry PROS1 gene mutation. Case 1 received anticoagulation therapy for 3 months, and case 2 also received anticoagulation therapy for 3 months. During the 1 year follow-up, no new thrombotic events and no adverse reactions such as bleeding were observed in both patients.**

Conclusions: **For children with pulmonary embolism without clear risk factors, PSD should be considered, and protein S activity should be tested before receiving anticoagulant drugs.**

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KEYWORDS

pulmonary embolism, child, PROS1, variations

CASE PRESENTATION

Case 1

A 10-year-old girl came to the emergency department of our hospital because of cough and chest pain. She had right chest pain 4 days ago, which was obvious at the end of inspiration and cough. Chest CT showed multiple abnormal density shadows in both lungs and consolidation of the lower lobe of the right lung. There was pain and swelling in the left leg 2 months ago, the pain was completely relieved 1 month ago with no therapy. Grandfather had DVT at the age of 70 and her father also was diagnosed with DVT at the age of 44. Both of them improved quickly after anticoagulation treatment. They denied the history of other definite genetic diseases. Fibrinogen, plasma prothrombin time, and activated partial thromboplastin time were normal, but D-dimer was > 5.0 mg/L, and pulmonary embolism was

highly suspected. Computed tomography pulmonary angiography (CTPA) showed multiple segmental pulmonary embolisms and right lower pulmonary infarction in both lungs. Color Doppler ultrasound of the deep veins of the lower limbs was further performed to show thrombosis of the left femoral vein, popliteal vein. Echocardiography showed mild pulmonary hypertension (42.2 mmHg), and a small amount of regurgitation of mitral and tricuspid valves and pulmonary valves. She received anticoagulation therapy. The cough and chest pain of the proband were gradually relieved within 1 week. The screening of thrombotic risk factors showed that mycoplasma pneumoniae antibody IgM was negative; Antinuclear antibody 1:100 (granular), anti-double stranded DNA antibody, anti-extractable antinuclear antibody spectrum, anticardiolipin antibody, anti-β2-glycoprotein antibodies were negative; Protein S activity < 10% (reference value 49% - 125%), protein C activity, antithrombin activity, coagulation factors II, V, VII, VIII, IX, x, Xi, XII activity and von Willebrand factor were normal.

Case 2

An 8-year-old girl, the sister of case 1, was admitted to the emergency department of our hospital for the pain in her right leg one year later. The activity of protein S in outpatient screening showed 8%, and the coagulation function showed that D-dimer was 3.08 mg/L. The color Doppler ultrasound showed thrombus in the right external iliac vein and femoral vein.

Screening of protein S activity of family members: 36% of father, 26% of mother, 28% of another sister and 99% of aunt of case 1. The mother, another sister, grandmother and aunt of the proband had no history of thrombosis. After obtaining the consent of the parents of the above two patients, the whole exome gene sequencing of the pedigree showed that case 1 carried PROS1 gene complex heterozygous variants c.200a>c (p.e67a) and c.-168c>t, which were inherited from their father and mother, respectively, and confirmed by Sanger sequencing (Figure 1). According to the variation classification standard of the American Society of Medical Genetics and Genomics Guidelines. These two gene variations are classified as pathogenic variations. Sanger sequencing found that case 2 and case 1 genotypes were the same, case 1 sister and grandfather carried the c.200a>c (p.e67a) mutation, and case 1 aunt and grandmother did not carry the PROS1 gene mutation. Case 1 received anticoagulation therapy for 3 months, and case 2 also received anticoagulation therapy for 3 months. During the 1 year follow-up of, no new thrombotic events and no adverse reactions such as bleeding were observed in both patients.

DISCUSSION

Pulmonary embolism in children is rare and is easily misdiagnosed and missed. Therefore, for patients with cough and obvious chest pain, especially when chest pain is located on one side, the possibility of pulmonary embolism should be considered. D-dimer is a good screening indicator, and CTPA is the preferred diagnostic method [1]. There are many inducements for pulmonary embolism in children. For patients without clear risk factors, it is necessary to carry out relevant tests on infection, immunity, tumor and thrombosis, and investigate potential diseases [1,2].

PSD is a thromboembolic disease. The incidence rate of PSD in Asia is significantly higher than that in Europe and the United States. Protein S, located in 3q11 PROS1 gene, is a vitamin K-dependent glycoprotein, which can help activate protein C inactivate coagulation factors Va and VIIIa, thus playing an anticoagulant role. PROS1 gene defect leads to abnormal quantity or function of protein S, which leads to an increase in thrombosis propensity [2]. The autosomal dominant PSD (omim: 612,336) caused by heterozygous variation of its clinical phenotype in online Mendelian inheritance (omim) is the most common clinical phenotype. The risk of thrombosis in patients with heterozygous variation is 2.5 - 11.0 times higher than that in normal people. The autosomal recessive PSD (omim: 614,514) caused by homozygous or compound heterozygous variation is rare and usually presents as early-onset severe thrombosis [1-3]. In this family, case 1 and case 2 were PSD children caused by a complex mutation, and the protein S activity was less than 10%. The clinical manifestation was venous thromboembolism, which began at the early stage of development. Both parents and grandparents were heterozygous patients, and the activity of protein S decreased to about 30%. Among them, their father and grandfather developed thrombosis at the age of 44 and 70, respectively, while their mother had no symptoms, which showed that patients with heterozygous mutations were relatively old at the time of onset, with different clinical severity, and were prone to disease when combined with other risk factors of thrombosis.

We searched PubMed database for "protein S deficiency", "PROS1", "homozygous" and "complex heterozygous". The literature from the establishment of the database to March 2023 was retrieved, and 12 PSD patients caused by homozygous or compound heterozygous variation of PROS1 gene were finally included [3-8]. The clinical manifestations of 3 neonates included fulminant purpura and intracranial hemorrhage. The onset age of the other 9 patients was 7 - 35 years old, and the median age was 15 years old. Among them, 8 cases showed deep venous thrombosis of lower limbs with or without pulmonary embolism, and 1 case showed intracranial venous sinus thrombosis. Protein S activity was detected in 10 patients, all < 10%. Homozygous variation of PROS1 gene was detected in 4 patients, and compound

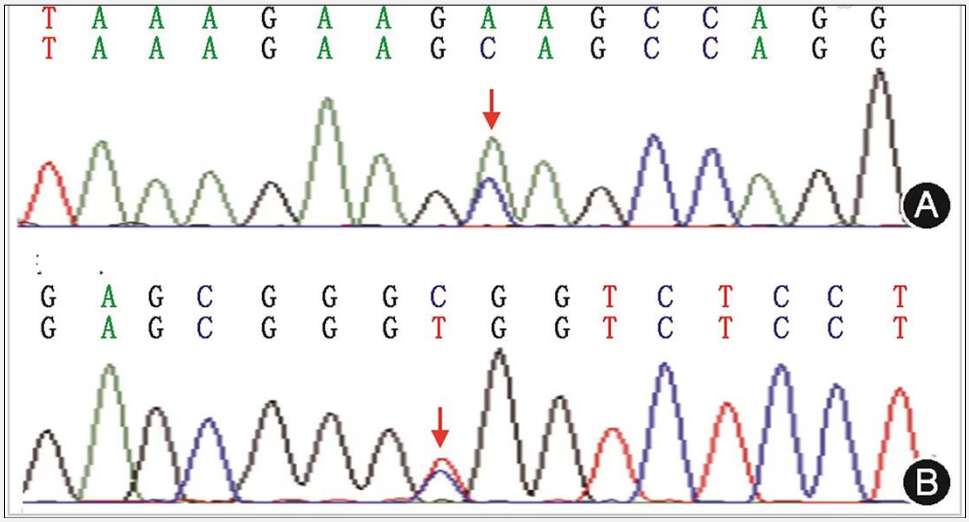

Figure 1. Sequencing results of PROS1gene in probands with hereditary protein S deficiency.

Probands carry complex heterozygous variants of PROS1 gene c.200a>c (p.e67a) (A) and c.-168c>t (B).

heterozygous variation was detected in the other 6 patients. There are 15 gene mutation sites, and missense mutation is the common [8]. Among the 9 non-neonatal patients, 7 patients received heparin or low-molecular-weight heparin treatment, and then 4 patients received warfarin treatment, and 3 patients received rivaroxaban treatment (including 2 patients in this group).

In the past, PSD patients with homozygous or compound heterozygous mutations mostly showed severe thromboembolism at early onset, such as fulminant purpura in newborns. Therefore, it has been suggested that when the activity of protein S is less than 10%, PSD caused by complex heterozygous variants should be highly suspected. The activity of protein S is easily affected by oral anticoagulants (including warfarin, rivaroxaban and other oral anticoagulants), so it needs to be tested before receiving oral anticoagulants [8].

Homozygous or compound heterozygous PSD patients with thrombus receive different courses of treatment, but many patients have thrombus recurrence after drug withdrawal [6], so long-term anticoagulation treatment is recommended. Two cases emphasized that although pulmonary embolism in children is rare, it can also occur, and pediatricians should pay attention to it. For children with pulmonary embolism without clear risk factors, PSD should be considered, and protein S activity should be tested before receiving anticoagulant drugs.

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Learning Points:

1. In children with pulmonary embolism without clear risk factors, PSD should be considered.
2. Protein S activity should be tested before receiving anticoagulant drugs.
3. Children with PSD may need to receive long-term anticoagulation, and the selection of anticoagulant drugs also needs to be carefully considered.

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There were no conflicts of interest nor legal liability in our report.

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