Neurology Asia 2025; 30(4) : 1237 – 1244

CASE REPORTS

PAI-1 4G/5G mutation leads to acute mountain sickness with reversible splenial lesion syndrome and intracranial arteriovenous thrombosis: A case report and literature review

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Abstract

Acute mountain sickness (AMS) rarely manifests with concurrent reversible splenial lesion syndrome (RESLES), cerebral venous sinus thrombosis (CVST), and bilateral watershed infarctions. We present the first reported case linking these neurological complications to a plasminogen activator inhibitor-1 (PAI-1) 4G/5G promoter mutation under hypoxic stress. A 23-year-old male developed AMS with encephalopathy and lower limbs weakness following rapid ascent to 3,000m. Critical findings included: 1) Corpus callosum splenium lesions showing RESLES-specific magnetic resonance imaging (MRI) evolution; 2) CVST involving straight and transverse sinuses on magnetic resonance venography (MRV); 3) Watershed infarcts at arterial borderzones. Thrombophilia screening revealed a heterozygous PAI-1 4G/5G mutation, with elevated hematocrit (50.3%) and D-dimer (4.14 μg/mL). Combined anticoagulation (low-molecular-weight heparin transitioning to dabigatran) and hyperbaric oxygen achieved partial venous recanalization at 1-month follow-up, with complete RESLES resolution. In conclusion, this case highlights the complex interplay between genetic factors (PAI-1 mutation), high-altitude hypoxia, and the development of rare cerebrovascular complications, providing valuable insights for clinical diagnosis and treatment.

Keywords: Acute mountain sickness, PAI-1 polymorphism, reversible splenial lesion syndrome, cerebral venous thrombosis, watershed cerebral infarction

INTRODUCTION

Cerebral venous and sinus thrombosis (CVST) is a rare and special type of cerebrovascular disease, with a high mortality and disability rate. Its etiology is complex. The heterozygous mutation of 4G/5G in the promoter region of plasminogen activator inhibitor-1 (PAI-1) is a hereditary thrombophilia, which is associated with an increased risk of venous thrombosis.[1] Reversible splenial lesion syndrome (RESLES) often presents with clinical manifestations of encephalitis or encephalopathy. Imaging is characterized by high signals on T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) sequences, isointense or slightly hypointense signals on T1-weighted imaging (T1WI), and restricted diffusion on diffusion-weighted imaging (DWI) in the splenium of the corpus callosum (SCC). Moreover, the imaging abnormalities of most patients are completely reversible within a few weeks to months.[2] RESLES is most commonly

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Date of Submission: 28 June 2025; Date of Acceptance: 4 July 2025

https://doi.org/10.54029/2025sir

associated with epilepsy and antiepileptic drugs, infections and metabolic disorders. Cases of RESLES caused by acute mountain sickness (AMS) are rare. This article reports a case of AMS complicated by RESLES, bilateral watershed cerebral infarction, and CVST due to a PAI-1 gene mutation, aiming to provide a reference for clinical diagnosis and treatment.

CASE REPORT

A 23-year-old male was admitted to the hospital with chest tightness and breathlessness for 7 days and bilateral lower limb weakness for 4 days. Seven days ago, after arriving directly from a plain area to Qinghai by plane, the patient developed discomfort such as chest tightness, shortness of breath, palpitations, and rapid breathing. After receiving oxygen inhalation, the symptoms improved slightly.

Six days ago, he suffered from chest tightness and breathlessness again with loss of consciousness and was then sent to the local hospital.

Blood routine tests showed that the red blood cell (RBC) count was 5.51*10^12/L (normal range: 3.8-5.1*10^12/L), hemoglobin (HB) was 170 g/L (normal range: 115-150 g/L), and hematocrit (HCT) was 48.8% (normal range: 35-50%). Chest computed tomography (CT) showed pulmonary edema. Considering the high possibility of altitude sickness, the patient was treated with hyperbaric oxygen, mannitol, and his consciousness gradually recovered. 4 days ago, the patient developed weakness in both lower extremities and was unable to stand or walk independently. He came to our hospital for further diagnosis and treatment. The patient had no previous significant medical history and denied having hypertension, diabetes, coronary heart disease, infectious diseases, or a family history of genetic diseases. The neurological examination showed that the muscle strength of both lower extremities was grade 4, the heel-knee-tibia test was not stable and accurate, and the rest of the examination results were normal.

After admission, blood routine tests showed that RBC was 5.52*10^12/L, HB was 170 g/L, and HCT was 50.3%. The D-dimer level was 4.14 μg/ml. Chest CT suggested possible bilateral pulmonary inflammation combined with pulmonary edema. Brain CT showed increased density in the bilateral internal cerebral veins and the straight sinus (Figure 1A). Brain magnetic resonance imaging (MRI) showed multiple abnormal signals in the bilateral corona radiata, semi-oval centers, and the splenium of the corpus callosum, suggesting bilateral watershed cerebral infarction (Figures 1B-C). Brain susceptibility-weighted imaging (SWI) showed

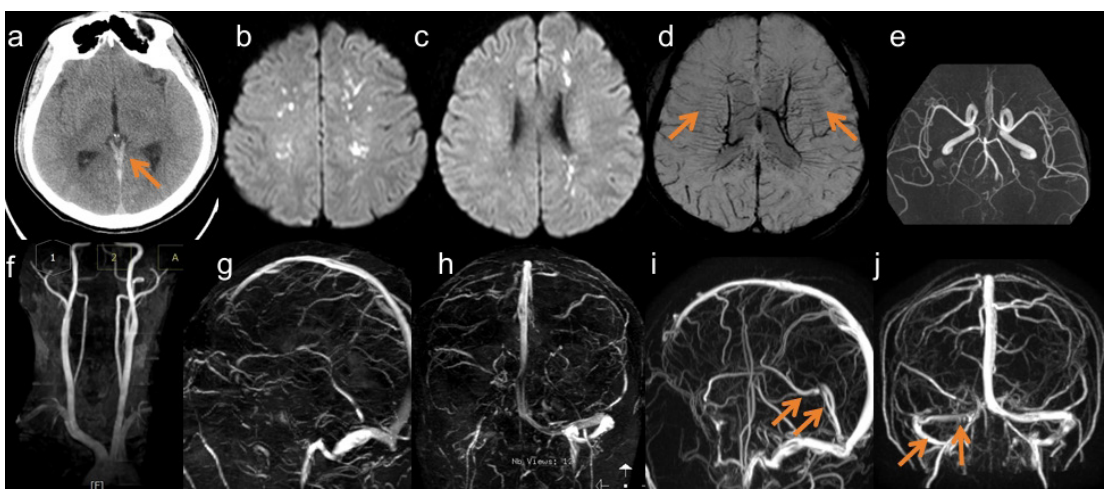

Figure 1. Brain CT and MR findings. a. Brain CT shows high signals in the internal cerebral veins, great cerebral vein, and straight sinus (orange arrow); b-c Brain MRI shows bilateral watershed infarction; d Brain SWI shows multiple abnormal vascular flow-void signals, the "brush sign" (orange arrows); e-f Brain MRA and neck MRA show no obvious abnormalities; g-h Brain MRV on December 1, 2024, shows that the transverse sinus and right sigmoid sinus are not visualized, the straight sinus is poorly visualized; i-j Follow-up brain MRV after treatment shows partial recanalization of the straight sinus, right transverse sinus, and sigmoid sinus (orange arrows). Abbreviations: CT, computed tomography; MR, magnetic resonance; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; SWI, susceptibility-weighted imaging.

multiple abnormal vascular flow-void signals in the bilateral semi-oval centers (Figure 1D). Brain and neck magnetic resonance angiography (MRA) showed no obvious abnormalities (Figures 1E-F). Brain magnetic resonance venography (MRV) on suggested possible thrombotic occlusion of the straight sinus, right transverse sinus, and sigmoid sinus (Figures 1G-H). Echocardiogram showed a roughly normal echocardiogram. The patient's ANA spectrum, ANCA, and antiphospholipid antibody spectrum were all negative, and anti-streptolysin O and rheumatoid factor were both within normal limits. Genetic screening for thrombophilia was performed on three mutation sites in three genes of the patient, including FV(Leiden) (G1691A), PAI-1 (-675 4G>5G), and MTHFR (C677T). A 4G/5G gene mutation in the promoter region of PAI-1 was detected.

After admission, the patient was given comprehensive treatment, including aspirin for anti-platelet aggregation, low-molecular-weight heparin for anticoagulation, atorvastatin for lipid-lowering, as well as treatments for improving blood circulation, hyperbaric oxygen therapy, dehydration, and anti-infection. After treatment, the patient's symptoms of chest tightness, shortness of breath, and weakness in both lower extremities completely improved. After discharge, the patient was prescribed oral dabigatran 110mg twice a day. Two weeks after discharge, follow-up brain MRV showed partial recanalization of the straight sinus, right transverse sinus, and sigmoid sinus (Figures 1I-J). Repeat brain MRI showed that the signal in the SCC had completely returned to normal, supporting the diagnosis of RESLES (Figure 2).

DISCUSSION

Cases of AMS complicated by RESLES, CVST, and bilateral watershed cerebral infarction are extremely rare. Here, we report a case where these complications in AMS are attributed to a 4G/5G gene mutation in the promoter region of PAI - 1. The patient in this case was a 23-year-old male who developed a series of rare and complex neurological complications, including RESLES, CVST, and bilateral watershed cerebral infarction, due to AMS. After arriving at a high-altitude area, the patient developed typical AMS symptoms such as chest tightness and shortness of breath, which later progressed to loss of consciousness and weakness in both lower extremities. After admission, imaging examinations suggested pulmonary edema, bilateral watershed cerebral infarction, and lesions in the SCC. MRV further confirmed the presence of CVST. Genetic testing revealed a 4G/5G heterozygous mutation in the

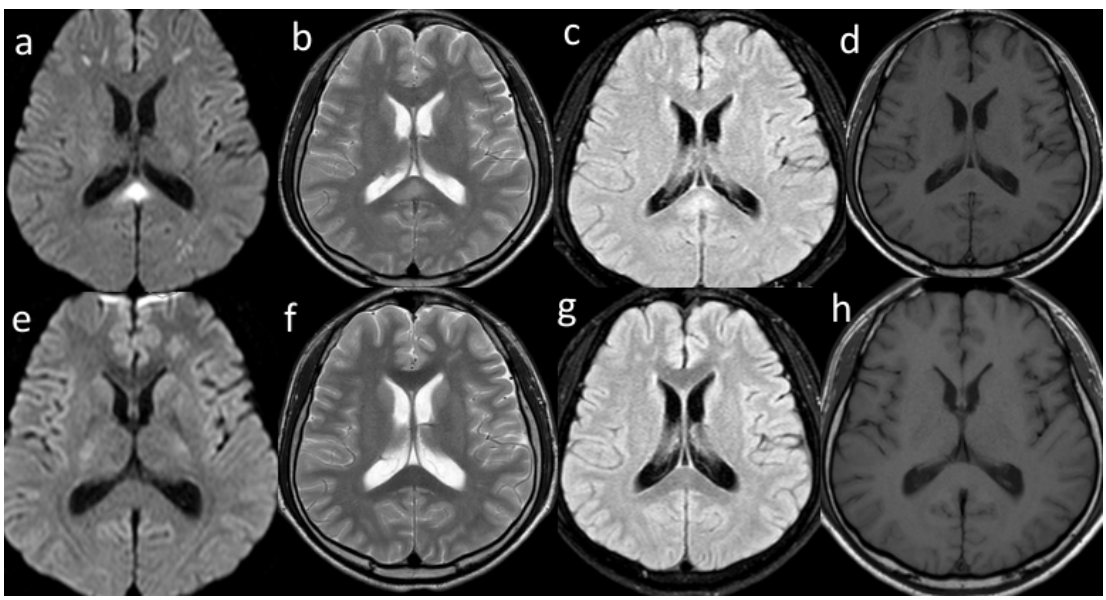

Figure 2. MRI evolution of RESLES. a-d: Admission imaging demonstrates characteristic findings: (a) DWI hyperintensity, (b) T2WI mild hyperintensity, (c) FLAIR hyperintensity, and (d) T1WI isointensity in the splenium of the corpus callosum. e-h: Complete resolution of all signal abnormalities at 1-month follow-up. Abbreviations:DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; RESLES, reversible splenial lesion syndrome; SWI, susceptibility-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

promoter region of PAI-1, indicating hereditary thrombophilia, which may be an important genetic background for the occurrence of CVST and watershed cerebral infarction. After comprehensive treatment with anticoagulation, anti-platelet aggregation, improvement of blood circulation, and hyperbaric oxygen therapy, the patient's symptoms completely improved, and follow-up imaging showed partial recanalization of the occluded venous sinuses and complete recovery of the lesions in the SCC.

CVST accounts for less than 1% of all strokes and can cause clinical manifestations such as severe headache, focal epileptic seizures, and limb paralysis[3], and can be life-threatening in severe cases. The etiology of CVST is complex and diverse. Current studies have found that the polymorphism of the PAI-1 gene is associated with the occurrence of CVST.[4] The PAI-1 gene is located in the 7q21.3-q22 region of human chromosome[7]. PAI-1 is mainly produced in endothelial cells and belongs to the serine protease inhibitor superfamily. It mainly regulates fibrinolysis and thrombosis by inhibiting the activities of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA).[5] It is the main regulator of plasmin activation in the body. The genotypes of PAI-1 include 4G/4G, 4G/5G, and 5G/5G, which regulate the expression level of PAI-1. Studies have shown that the PAI-1 4G/4G genotype or the 4G allele is associated with increased transcription of the PAI-1 gene.[6-8] The plasma levels of PAI-1 in individuals with 4G/4G and 4G/5G genotypes are elevated. The increased activity of PAI-1 in the body can inhibit normal fibrinolysis, thereby significantly triggering fibrin deposition and leading to thrombosis.[6,9] In addition, the high expression of PAI-1 is closely related to the hypercoagulable state of blood[10] and can also lead to dysfunction of endothelial cells.[11] Endothelial cells are located on the inner surface of blood vessels and play a key role in maintaining vascular homeostasis. Dysfunction of endothelial cells can lead to a pre-thrombotic state. Moreover, PAI-1-mediated endothelial cell dysfunction may involve changes in the expression of adhesion molecules, impairment of nitric oxide production, and increased oxidative stress. These changes can promote platelet adhesion and aggregation, as well as the activation of the coagulation cascade.[12] Therefore, the risk of arterial and venous thrombosis is significantly increased.[13,14] However, to date, case reports on the association between the PAI-1 4G/4G or 4G/5G genotype and CVST are rare. To comprehensively review the existing clinical evidence in this field, this study systematically searched the PubMed, CNKI, and Wanfang databases and conducted a retrospective analysis of relevant literature. After screening, a total of 4 eligible articles were included, and the case data are summarized in Table 1.

AMS is a common clinical syndrome in high-altitude areas. It is a series of clinical syndromes that occur when the human body rapidly enters an area above 3,000 meters above sea level and is exposed to a hypoxic environment, due to incomplete adaptation of the body to the hypoxic environment. Common symptoms include headache, dizziness, fatigue, insomnia, nausea, and vomiting. In severe cases, it can progress to high-altitude pulmonary edema and high-altitude cerebral edema, which can be life-threatening.[19] Cases of AMS complicated by RESLES are rare. On MRI, RESLES is manifested as solitary, oval lesions in the SCC, with isointense or slightly hypointense signals on T1WI, slightly hyperintense signals on T2WI and FLAIR, hyperintense signals on DWI, and significantly hypointense signals on the ADC. There is usually no obvious enhancement on contrast-enhanced scanning[20], and the lesions completely disappear within a few weeks or months. The possible mechanisms of AMS-induced RESLES are as follows: (1) Hypoxia-induced blood-brain barrier damage: In a high-altitude hypoxic environment, the body dilates cerebral blood vessels and increases cerebral blood flow to adapt to hypoxia. However, continuous hypoxic stimulation can lead to dysfunction of cerebral vascular endothelial cells and changes in the expression of tight-junction proteins, thus disrupting the integrity of the blood-brain barrier. Studies have shown that acute hypoxic exposure can cause oxidative stress in cerebral vascular endothelial cells, activate inflammatory signaling pathways, and increase the permeability of the blood-brain barrier.[19] (2) Energy metabolism disorders: Neurons in the splenium of the corpus callosum have a high demand for energy, and their metabolic substrates mainly rely on aerobic oxidation of glucose. When AMS occurs, hypoxia blocks the aerobic oxidation process of glucose, enhances anaerobic glycolysis, produces a large amount of lactic acid, and causes intracellular acidosis. At the same time, insufficient energy impairs the function of ion pumps on the cell membrane, such as reducing the activity of sodium-potassium ATPase, leading to the accumulation of sodium ions in the cell and the influx of water into the cell, causing cytotoxic edema.[21-23] (3) Neurotransmitter imbalance:

Table1: Reported case of cerebral venous sinus thrombosis associated with PAI-1 genotype

Patient	Sex	Age (years)	Occluded venous sinus	PAI-1 genotype	Treatment	Prognosis
1[15]	Female	22	Upper sagittal sinus, straight sinus, transverse sinus	4G/4G	Heparin, followed by anticoagulation with warfarin. Intracranial thrombectomy, bilateral optic nerve openings, and ventriculoperitoneal shunts were also performed	Cerebral venous sinus recanalization. However the patient had bilateral optic neuropathy and loss of vision. The patient's neurological status remained stable with continued anticoagulatio-n with warfarin
2[16]	Male	38 weeks	Bilateral transverse sinuses	4G/5G	Low molecular heparin 150 U/kg twice daily and dose adjusted to maintain anti-Xa factor levels at 0.5-1.0 U/ml. Anticoagulation lasts two months	The thrombus in the head subsided after 8 weeks, and neurologic function was normal on follow-up at 6 months of age
3[17]	Male	40	Right transverse	4G/4G	Enoxaparin, sequential long-term anticoagulation with dabigatran	Acute myocardial infarction occurred 3 weeks after discharge, heparin anticoagulatio-n was used again, and the hospital was discharged to warfarin long-term anticoagulatio-n, and the INR was maintained at 2-3
4[18]	Male	34	Superior sagittal sinus	4G/4G	Initial treatment with low molecular heparin-enoxapa-rin 60 mg every 12 hours followed by oral anticoagulant	Discontinuation of anticoagulatio-n after 3 years without recurrence of arterial or venous thrombosis

Studies have found that the release of excitatory neurotransmitters such as glutamate in the brain of AMS patients is increased, while the inhibitory neurotransmitter γ-aminobutyric acid is relatively insufficient.[24] Excessive excitation of glutamate can lead to excessive neuronal discharge, causing neurotoxic effects and resulting in neuronal edema and damage. (Figure 3)

It is worth noting that in addition to RESLES, this patient also had CVST and bilateral watershed cerebral infarction. The possible mechanisms are as follows: (1) In a high-altitude environment, the oxygen partial pressure decreases, leading to hypoxia in the body. Hypoxia can trigger a series of physiological reactions, including increased blood viscosity, secondary polycythemia, and abnormal coagulation function. For example, the patient in this case had polycythemia on admission, and the D-dimer level was significantly higher than normal. These factors together increase the risk of arteriovenous thrombosis.[25] (2) Hypoxia may slow down the cerebral venous blood flow and increase the venous pressure, further promoting the occurrence of CVST.[19] (3) In a high-altitude environment, hypoxia and hypotension can lead to a decrease in cerebral perfusion pressure.

The watershed area refers to the marginal zone between adjacent arterial blood-supply areas in the brain. These areas are particularly sensitive to changes in blood perfusion. Therefore, watershed infarction is likely to occur when the cerebral perfusion pressure drops rapidly. (4) Hypoxia and a hypercoagulable state may lead to the formation of micro-emboli. These emboli may block the small blood vessels in the watershed area. Coupled with a decrease in cerebral perfusion pressure and a reduced embolus clearance rate, watershed infarction is triggered.[26] (5) CVST can lead to obstruction of cerebral venous return, causing increased intracranial pressure and decreased cerebral perfusion pressure, further aggravating the ischemia in the watershed area. (6) The patient in this case had a 4G/5G gene mutation in the promoter region of PAI-1, indicating hereditary thrombophilia, which is an important genetic background for the occurrence of CVST and watershed cerebral infarction in the patient. To date, through systematic searches of the PubMed, CNKI, and Wanfang databases, this study has not found cases of AMS complicated by both venous sinus thrombosis and cerebral infarction, and only cases of AMS-induced CVST have been reported. (Figure 3)

Anticoagulation remains the cornerstone of CVST treatment, with heparin and warfarin traditionally serving as first-line agents. However, the 2011 AHA/ASA Guidelines[27] and the 2017 ESO Guidelines[28] did not recommend the use of direct oral anticoagulants (DOACs), and the 2019 Chinese guidelines only state that "dabigatran may be considered in patients unsuitable for warfarin".[29] In recent years, the application of DOACs in CVST has drawn increasing attention. The RE-SPECT CVT trial[30], a prospective, multicenter randomized controlled study, enrolled 120 stable CVT patients and compared dabigatran (150 mg twice daily) with dose-adjusted warfarin (INR 2–3). No recurrent venous thromboembolism (VTE) events occurred in either group, with comparable bleeding risks and recanalization rates (60% vs. 67.3%). While the findings suggest similar safety and efficacy, the limited sample size prevented conclusions regarding non-inferiority or superiority. The ACTION-CVT study[31], an international retrospective cohort analysis, included 845 eligible patients between 2015 and 2020. It found that DOACs and warfarin had similar rates of recurrent thrombosis, mortality, and venous recanalization. Notably, the DOAC group had a significantly lower risk of major

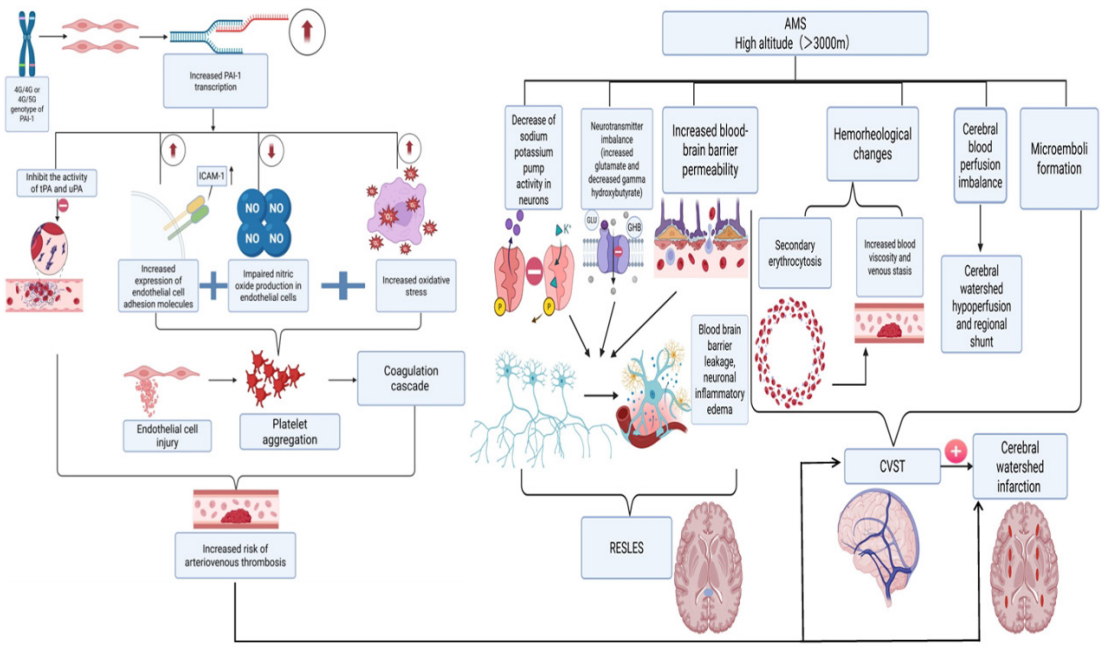

Figure 3. Pathophysiological interplay between PAI-1 4G/5G mutation and AMS underlying RESLES, CVST and bilateral watershed infarctions. Abbreviations: AMS, acute mountain sickness; CVST, cerebral venous sinus thrombosis; ICAM-1, intercellular cell adhesion molecule-1; GHB,Gamma-hydrobutyrate; GLU, glutamate; RESLES, reversible splenial lesion syndrome.

bleeding (HR 0.35; P = 0.02), though the study was limited by treatment selection bias and follow-up loss. The SECRET trial[32], a phase II multicenter randomized open-label study, enrolled 55 newly diagnosed symptomatic CVT patients and compared rivaroxaban with standard anticoagulation. Although the rivaroxaban group had a numerically higher bleeding rate, it remained within expected ranges, and functional outcomes were similar, indicating the feasibility of DOAC use in this setting. The CHOICE CVT trial[33], published in 2024, was a single-center open-label study that randomized 89 Chinese CVT patients to dabigatran or warfarin after 10–15 days of low-molecular-weight heparin. No significant differences were observed in CVT/DVT recurrence, major bleeding, or venous recanalization, though the study's generalizability was limited by its design. In summary, while the role of DOACs in CVST remains controversial, emerging evidence suggests comparable efficacy and safety to warfarin. Due to small sample sizes and design limitations, further large-scale, high-quality randomized controlled trials are needed to define their optimal use across different CVST populations. In this case, the patient received subcutaneous low-molecular-weight heparin during hospitalization, followed by dabigatran after discharge. One month later, follow-up imaging demonstrated satisfactory recanalization of the previously occluded venous sinuses.

In conclusion, this case represents a rare instance of AMS-associated RESLES, bilateral watershed cerebral infarction, and CVST, with a PAI-1 4G/5G gene mutation serving as an important genetic predisposing factor. The complex pathophysiological mechanisms underlying these concurrent conditions involve hypoxia-induced changes in blood-brain barrier function, energy metabolism, neurotransmitter balance, as well as alterations in blood rheology and coagulation. The current understanding of the role of PAI-1 gene polymorphisms in CVST and related cerebrovascular events is still limited, and more research is needed to fully elucidate the relationship. Regarding treatment, although anticoagulation is the mainstay for CVST, the optimal choice of anticoagulant, especially the use of DOAC, remains controversial due to the limitations of existing clinical trials. This case emphasizes the importance of considering genetic factors in patients with high-altitude-related cerebrovascular complications and provides a reference for future clinical practice and research in this field.

DISCLOSURE

Ethics: Case submission approved by Qingdao Municipal Hospital Ethics Committee.

Data availability: Data are available from the corresponding author upon reasonable request, subject to approval by the institutional review board.

Conflict of interest: None

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