An unusual cause of cerebral venous sinus thrombosis

Paroxysmal nocturnal hemoglobinuria

Sheng Bi, *MD,* ***Jia Fan,*** *MD,* ***Jing Dong,*** *MD,* ***Qun Liu,*** *MD.*

ABSTRACT

يعد التخثر الجيبي الوريدي الدماغي الذي يتسبب في حدوثه مرض البيلة الهيموغلوبينية الانتيابية الليلية من الأمور النادرة الحدوث. نستعرض في هذا المقال حالة مريضة تبلغ من العمر 44 عاماً، وقد جاءت إلى المستشفى بعد إصابتها بالصداع، والغثيان، والنوبات التشنجية التي استمرت لمدة يومين، ومن ثم تلتها الإصابة بشلل تود. لقد شُخصت حالتها على أنها مُصابة بمرض البيلة الهيموغلوبينية الانتيابية الليلية لمدة 4 سنوات، غير أن تصوير الأوردة بالرنين المغناطيسي كشف عن وجود تخثر واسع الانتشار في الجيب الوريدي الدماغي. وهكذا تم علاجها بموانع التخثر، وقد كانت النتائج إيجابية. نسلط الضوء في هذا المقال على مرض البيلة الهيموغلوبينية الانتيابية الليلية وإمكانية تسببه في حدوث التخثر الجيبي الوريدي الدماغي، كما أننا نلفت النظر إلى وجوب معالجة هذا التخثر الذي يسببه مرض البيلة الهيموغلوبينية الانتيابية الليلية على انفراد.

Cerebral venous sinus thrombosis caused by paroxysmal nocturnal hemoglobinuria is uncommon. Our case is a 44-year-old woman who presented with a 2 day history of headaches, nausea, and seizures followed by a Todd's paresis; she had been diagnosed as paroxysmal nocturnal hemoglobinuria for 4 years. A magnetic resonance venography revealed extensive thrombosis of the cerebral venous sinus. She received antithrombotic treatment with a good outcome. We highlight paroxysmal nocturnal hemoglobinuria as the reason for the cerebral venous sinus thrombosis. The treatment of cerebral venous sinus thrombosis caused by paroxysmal nocturnal hemoglobinuria should be individualized.

Neurosciences 2011; Vol. 16 (3): 267-269

From the Department of Neurology (Bi, Dong, Liu) First Hospital, and the Department of Neurology (Fan), Second Hospital, Jilin University, Changchun, China.

Received 15th December 2010. Accepted 27th March 2011.

Address correspondence and reprint request to: Dr. Sheng Bi, Department of Neurology, First Hospital, Jilin University, Changchun 130000, China. Tel. +86 15143171390. E-mail: bishengbs_1981@yahoo.com.cn

Cerebral venous sinus thrombosis (CVST) presents with a wide spectrum of symptoms and signs including headache, focal neurological deficits, seizures, and coma. The onset may be acute, subacute, or insidious. The clinical outcome is highly variable, patients may have complete functional recovery or may develop severe and lasting neurological deficits. There are many causes for this disease.[1] Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, clonal disorder of hematopoietic cells. It is associated with anemia, intravascular hemolysis, and venous thrombosis. Venous thrombosis has been reported in all organs except the spinal cord and bone marrow. A CVST is a rare and late presentation of PNH.[2] Herein, we describe a woman who developed CVST as the thrombotic complication of previously diagnosed PNH. Our objective in presenting this particular case is to highlight paroxysmal nocturnal hemoglinuria as the reason for cerebral venous thrombosis.

Case Report. A 44-year-old woman was admitted to our department with chief complaints of headaches, nausea, and seizures followed by a Todd's paresis. She also had a history of progressive, intense bitemporal headache, nausea, and several episodes of seizures followed by a Todd's paresis from 2 days before admission. On examination, she was of average built, afebrile with pulse rate of 90 per minute, and blood pressure of 130/80 mm Hg. The only objective finding on physical examination was bilateral papilledema. She had been diagnosed as PNH by hemolytic anemia, positive Ham test, and CD59 deficiency in erythrocytes for 4 years. She had had blood transfusion for anemia, and had not used any anticoagulation treatment to prevent thrombotic events. She had one child. A CT of the head excluded intracerebral hemorrhage on the first day after admission. The C-Reactive protein, antinuclear antibody, single-strand DNA, double-strand DNA, rheumatoid factor, and tumor marker were negative. She was treated with acyclovir, cefepime, and mannitol. Her headache and nausea gradually improved, lumbar puncture was

carried out after injecting mannitol on the third day after admission and showed clear rufous liquid with 340 mm H_2O of pressure. Laboratory tests of CSF gave the following results: protein 0.69g/L (normal range [NR] 0.15-0.45 g/L), chloride 118.9 mmol/L (NR 119-129 mmol/L), glucose 2.90 mmol/L, white blood cell count 2 $\times 10^6$/L, and red blood cell count (RBC) 2880 $\times 10^6$/L (normally no RBC) (fresh red blood cells and no tumor cell on observation). An MRI showed an infarction in the superior sagittal sinus territory (**Figure 1**). Magnetic resonance venography (MRV) demonstrated extensive thrombosis of the superior sagittal sinus with some visible small collateral veins (**Figure 2**). The results of magnetic resonance angiography (MRA) and carotid ultrasonography were normal (**Figure 3**). Venous sinus thrombosis was diagnosed. Further investigation showed RBC 2.13×10^{12}/L, (NR $3.5\text{-}5.0\times10^{12}$/L), hemoglobin 78 g/L (NR 110-150 g/L), platelets 42×10^9/L (NR $100\text{-}300\times10^9$/L), and platelet anti aggregation with aspirin (100 mg/d) was instituted. She was treated with subcutaneous low molecular weight heparin. The heparin dosage was reduced to avoid hemorrhagic complications. She was prescribed oral warfarin after the subcutaneous low molecular weight heparin international normalized ratio (INR) was maintained at 3-4. She was treated with blood transfusion. At 3-month follow-up, she was discharged in a good condition and was advised bone marrow transplantation.

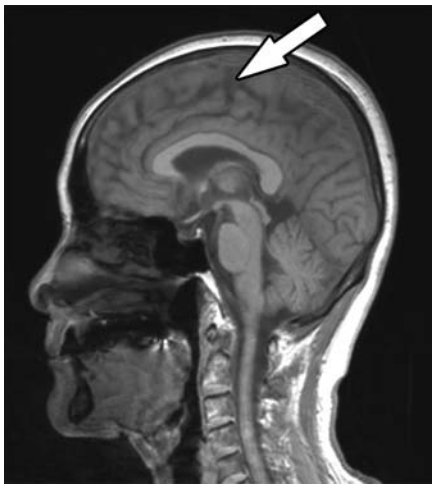

Figure 1 - Patient MRI showing infarction in the superior sagittal sinus territory (arrow).

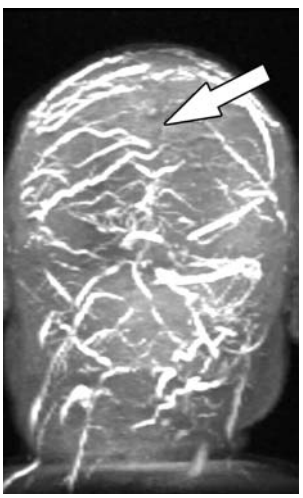

Figure 2 - Patient MR venography demonstrating extensive thrombosis of the superior sagittal sinus with some visible small collateral veins (arrow).

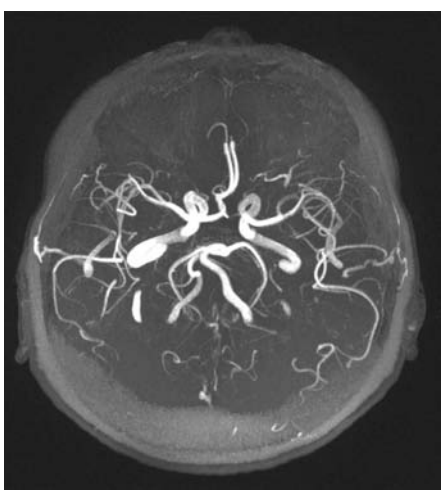

Figure 3 - Patient MR angiography showing normal arteries.

Discussion. There are many recognized causes and predisposing factors of CVST, the most common predisposing factors are pregnancy, puerperium, contraceptive pills, coagulopathies, and intracranial infections.[1] A study on CVST from a tertiary care center from India revealed that 18% of CVST patients occurred during the peripartum period.[3] Non-infective causes, which have increased in recent series, include red blood cell disorders, thrombocythemia, and coagulation disorders.[1] Thromboembolic phenomena in PNH are uncommon, and occur in around 5% of patients.[4] Thrombosis is more common in Europeans compared with Asians although its cause is unknown.[5] Venous thrombosis remains the independent predictor of death in PNH. In a review of 339 PNH patients with thrombosis, 25% died. The site of thrombosis in descending order of frequency is hepatic, pulmonary, mesenteric, and cerebral veins, and sinuses. The frequency of mortality because of thrombosis in PNH was 7% in CVST.[6]

Paroxysmal nocturnal hemoglobinuria is an acquired disease characterized by attacks of intravascular hemolysis and hemoglobinuria. The thrombotic tendency may be related to deficiency of the glycosyl phosphatidylinositol anchor protein. An increase in procoagulant and fibrinolytic activity, a decrease in the urokinase type

of plasminogen receptor on leucocytes and platelet dysfunction, and lack of complement regulatory proteins CD55 and CD59 on the surface of platelets have been suggested for thrombosis.[7] If venous thrombosis in PNH has occurred in an organ, it tends to recur at the same site, maybe because of residual endothelial proliferation in that area.[8]

Treatment of CVST includes supportive or symptomatic measures such as hydration, appropriate antimicrobials, control of seizures with anticonvulsants, and control of intracranial pressure. The antithrombotic treatment modalities include heparin, oral anticoagulants, thrombolysis, and endovascular approaches. For management of CVST in the presence of PNH, heparin followed by warfarin is used, and INR is recommended to be maintained at 3-4 for an indefinite period.[4] Anticoagulation was inadvertently stopped, which resulted in extensive thrombosis.[2] A non-randomized study comparing urokinase thrombolysis with heparin in adults suggested a better functional outcome for the patients undergoing CVST, but a higher risk of hemorrhage.[9] Eculizumab is a humanized monoclonal antibody against terminal complement protein C5 that inhibits terminal complement activation and has emerged as the first effective therapy for PNH. Eculizumab also reduces thrombotic events in PNH.[10]

In summary, our case demonstrates CVST following a previously diagnosed PNH. This case is even more uncommon. The clinical symptoms and signs of CVST are variable. It is very often unrecognized on initial presentation. Our experience with this patient emphasizes that CVST should be suspected in any patient, especially in PNH with the symptoms of headache. The presence of venous thrombosis demands rapid intervention. Treatment of CVST caused by PNH should be individualized. The safety of the antithrombotic treatment should be considered.

Acknowledgments. *We are grateful to Y. Y. Gu, Professor at the Department of Radiology, First Hospital, Jilin University, for reviewing the figures.*

References

1. Allroggen H, Abbott RJ. Cerebral venous sinus thrombosis. ***Postgrad Med J*** 2000; 76: 12-15.
2. Misra UK, Kalita J, Bansal V, Nair PP. Paroxysmal nocturnal haemoglobinuria presenting as cerebral venous sinus thrombosis. ***Transfus Med*** 2008; 18: 308-311
3. Kalita J, Bansal V, Misra UK, Phadke RV. Cerebral venous sinus thrombosis in a tertiary care setting in India. ***QJM*** 2006; 99: 491-492.
4. Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. ***Blood*** 2005; 106: 3699-3709.
5. Rosse WF. Paroxysmal nocturnal hemoglobinuria as a molecular disease. ***Medicine (Baltimore)*** 1997; 76: 63-93.
6. Ziakas PD, Poulou LS, Rokas GI, Bartzoudis D, Voulgarelis M. Thrombosis in paroxysmal nocturnal hemoglobinuria: sites, risks, outcome. An overview. ***J Thromb Haemost*** 2007; 5: 642-645.
7. Cappellini MD. Coagulation in the pathophysiology of hemolytic anemias. ***Hematology Am Soc Hematol Educ Program*** 2007: 74-78.
8. Taylor SR, Hashida Y, Jaffe R. Venous thrombosis and endothelial proliferation in paroxysmal nocturnal hemoglobinuria. ***Pediatr Pathol*** 1989; 9: 757-764.
9. Wasay M, Bakshi R, Kojan S, Bobustuc G, Dubey N, Unwin DH. Nonrandomized comparison of local urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis. ***Stroke*** 2001; 32: 2310-2317.
10. Hillmen P, Muus P, Duhrsen U, Risitano AM, Schubert J, Luzzatto L, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. ***Blood*** 2007; 110: 4123-4128.

Related topics

Kajtazi NI, Zimmerman VA, Arulneyam JC, Al-Shami SY, Al-Senani FM. Cerebral venous thrombosis in Saudi Arabia. Clinical variables, response to treatment, and outcome. ***Neurosciences (Riyadh)*** 2009; 14: 349-354.

Fatehi F, Basiri K, Saadatnia M, Koleini N. Cerebral venous thrombosis associated with oligodendroglioma and pregnancy. ***Neurosciences (Riyadh)*** 2009; 14: 277-279.

Al-Said Y. Management of cerebral venous thrombosis. ***Neurosciences (Riyadh)*** 2004; 9: 62.