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Cerebral venous sinus thrombosis as a recurrent thrombotic event in a patient with heterozygous prothrombin G20210A genotype after discontinuation of oral anticoagulation therapy: How long should we treat these patients with warfarin?

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Abstract *Background* Cerebral venous sinus thrombosis is an uncommon condition with many clinical manifestations, and hereditary prothrombotic conditions such as factor Leiden V, deficiency of protein S, protein C and antithrombin III, as well as prothrombin gene mutation, may account for 10–15% of cases. To date, conflicting results have been reported for recurrent venous thrombosis in the patients with factor V Leiden and prothrombin G20210A mutation, since some studies have shown a higher risk for recurrent venous thrombosis in carriers of these two mutations than in non-carriers, and the last study showed higher risk only for carriers of double defect (homozygous or double heterozygous for this mutations).
Methods Case report is presented.
Results We report a case of cerebral sinus thrombosis as a recurrent thrombotic event in a patient with heterozygous prothrombin G20210A genotype after discontinuation of oral anticoagulation therapy.
Conclusion Since many facts are controversial, the use of secondary prophylaxis for thrombosis in these patients is still a matter of debate without clear consensus recommendation. Data on the risk of recurrent thrombotic events in thrombophilic patient is insufficient. The main unclear question concerning these patients is: how long and whom should we treat with long-term anticoagulant therapy as secondary prophylaxis of DVT? The problem for practitioner is that we do not have guidelines and precise recommendations for secondary thromboprophylaxis in this or similar cases. This case is remarkable for its favorable and quick outcome and its rarity, because CSVT is an uncommon condition and heterozygous prothrombin G20210A genotype was only found predisposing factor for CSVT. Further studies of risk of recurrent venous thrombosis in patients with heterozygous prothrombin G20210A genotype with the larger sample size are required.

Keywords Cerebral venous sinus thrombosis · Prothrombin gene G20210A mutation · Heterozygous · Warfarin anticoagulation therapy

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Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon condition with many clinical manifestations so many cases remain clinically undetected. Numerous conditions can cause or predispose to CVST like infective causes, systemic conditions such as connective tissue diseases, other granulomatous or inflammatory disorders, malignancies, pregnancy, puerperium, oral contraceptives, and various coagulation disorders, acquired or hereditary. Hereditary prothrombotic conditions such as factor Leiden V, deficiency of protein S, protein C and antithrombin III, as well as prothrombin gene mutation may account for 10–15% of cases of CVST [1, 2].

We report a case of cerebral sinus thrombosis as a recurrent thrombotic event in a patient with heterozygous prothrombin G20210A genotype after discontinuation of oral anticoagulation therapy.

Case report

A 37-years old man was admitted to Emergency Neurology Department because of severe headache with nausea and vomiting, lasting 2 days. He presented mild left hemiparesis (1/5), left hemihypestesia, with vision disturbance and photophobia. Further examination revealed bilateral temporal bloodless papilla. He has smoked 30 cigarettes daily for the last 15 years. The patient's family history was positive for venous thromboembolism (VTE), since his mother has had venous thrombosis of hand, and she died 2 years later because of myocardial infarction. His brother had distal deep venous thrombosis (DVT) of left leg, but both of them have refused testing for thrombophilia. At 35 years of age, the patient initially presented with proximal DVT of right leg. A thrombophilia screening performed at our institution identified the prothrombin G20210A mutation in a heterozygous state, so oral anticoagulant treatment with warfarin was performed at an INR of 2–3 for next 2 years. Since the patient condition was good without any signs of recurrent DVT, warfarin was discontinued, and ticlopidine at the dose of 250 mg bid orally was initiated in the therapy. After few days patient self-willingly discontinued this treatment, and 2 months later had complained of severe headache. Upon admission, computed tomography (CT) of the brain indicated CVST (Fig. 1). Digital subtraction angiography demonstrated no signal in the inferior parts of sagittal sinus, in the transverse, confluence and the straight sinus, and partial thrombosis in the frontal and parietal parts of superior sagittal sinus. Patient was transferred in the Intensive Care Unit and dose-adjusted intravenous heparin (24,000 ij/240 ml 0.9% NaCl, ≈1,000 ij/h) and symptomatic therapy were started. On the 5th day oral anticoagulant drug, warfarin was included in the treatment (maintained at the INR range of 2–3), and heparin was excluded after 8 days. On 12th day CT showed normal brain density, and improved picture of sinovenous thrombosis. Clinical recovery was noted (headache had completely disappeared after 3 weeks, and other neurological deficits disappeared after 1 week upon admission), and 2 weeks upon admission magnetic resonance imaging combined with magnetic resonance venography (Shimatzu EPIOS5 0.5 T) showed less blood flow in the middle part of superior sagittal sinus, and some better signal in the other parts of sinus. His condition was constantly improving and was discharged after 6 weeks from the admission without long-term sequelae, and with recommendation for long-term use of warfarin. Till now, two years later there was no recurrent thrombosis.

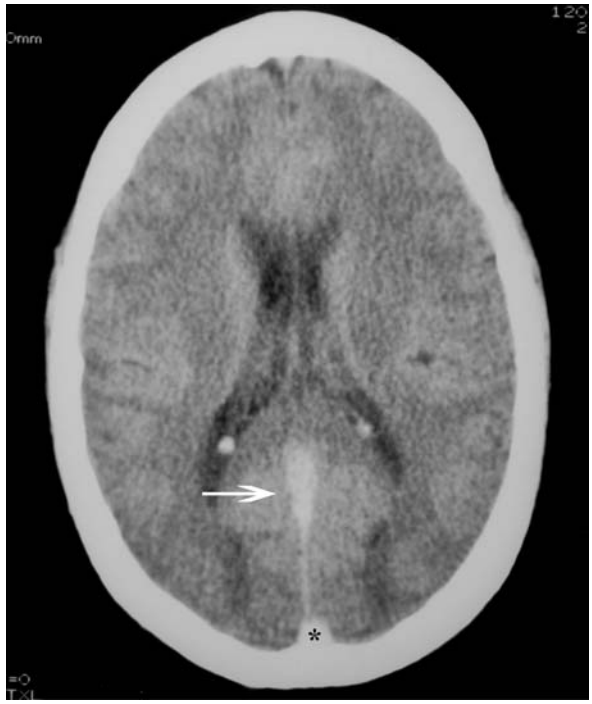

Fig. 1 Non-enhanced CT scan of the brain shows hyperdense thrombosed straight sinus (arrow) and Delta sign suggesting thrombosis of superior sagittal sinus (asterix)

Discussion

Venous thromboembolism is a multifactorial disease due to the interaction of various risk factors that can be genetic (e.g., inherited thrombophilia), acquired (e.g., age, neoplastic or autoimmune diseases, antiphospholipid antibodies), or transient (e.g., surgical interventions, fractures, trauma, prolonged immobilization) [3]. Hereditary thrombophilia are a heterogeneous group of genetic coagulation disorders such as antithrombin, protein C or S deficiency, dysfibrinogenemia, hyperhomocysteinemia, factor V Leiden and prothrombin gene mutation, mutation of methylene tetrahydrofolate reductase, elevated factor VIII, IX and XI, factor XII deficiency, elevated lipoprotein a, plasminogen deficiency, histidine-rich glycoprotein deficiency, thrombomodulin gene defect, and elevated tissue plasminogen activator [4, 5]. The prothrombin G20210A gene mutation (PT20210A) is associated

with an elevated risk of DVT (about 3-fold), although to a lesser degree than factor V Leiden is (3-fold to 8-fold elevations of risk) [6, 7]. There is wide variability in geographic distribution of the prothrombin gene mutation. The proportion of white individuals heterozygous for the allele varies from 0.7% to 6.5%, with the highest prevalence rates reported in Spain [8]. A review of data from 11 centers in Europe found a range of 0.7–4.0%, with the prevalence in southern Europe being almost twice as high as northern Europe (3.0% vs. 1.7%). In Croatia, the prevalence of factor V Leiden and PT20210A was in VTE patients 21% and 8% respectively, and 4% in healthy subjects for both mutations [9, 10].

Until now, there are few published reports about CVST associated with prothrombin gene mutation, as an isolated or combined thrombophilic factor [11–16]. These thrombophilic defects are well-established risk factor for a first episode of DVT, but their impact in DVT recurrence is less certain. To date, conflicting results have been reported for factor V Leiden and PTG20210A mutation, since some studies have shown a higher risk for recurrent DVT in carriers of these two mutations, and some of them not [17–19]. Recently, Gonzales-Porras et al. [20] have published very important and interesting study about risk of recurrent venous thrombosis in patients with prothrombin gene or factor V Leiden mutation. Their results indicate that carriers of a double defect, homozygous or double heterozygous for factor V Leiden and G20210A, have an increased risk after a first episode of DVT, but patients who were heterozygous for factor V Leiden or G20210a alone had a risk of recurrent DVT that similar to patients who had neither mutation (contrary to our case report), so extended secondary prophylaxis should be carefully considered. Based on these findings, long-term secondary thromboprophylaxis after first DVT episode seems to be of benefit for carriers of double defect. Also, they noted that patients with G20210A mutation were younger (38 vs. 49 years), they presented more secondary episodes of recent trauma or pregnancy than those without mutation, and had more DVT with pulmonary embolism. They also found that they were more serious among G20210A mutation carriers than factor V Leiden carriers. Patients with a proximal DVT have a higher incidence of recurrence than patients with distal DVT. Our case supports these findings because the patient was 37-years-old, with previous proximal DVT, and very serious secondary thrombotic event, but he wasn't carrier of a double defect. This case demonstrates that secondary thrombotic event appeared after discontinuation of oral anticoagulation therapy. We agree with authors that limitations to this study are its relatively small sample size and potential bias in referring patients.

Since many facts are controversial, the use of secondary prophylaxis for thrombosis in these patients is still a matter of debate without clear consensus recommendation. Data on the risk of recurrent thrombotic events in thrombophilic patient is insufficient. The main unclear question concerning these patients is: how long and whom should we treat with long-term anticoagulant therapy as secondary prophylaxis of DVT? The problem for practitioner is that we don't have guidelines and precise recommendations (evidence based medicine) for secondary thromboprophylaxis in this or similar cases. Last European Federation of Neurological Societies guideline on the treatment of CVST published in June 2006 is: indefinite anticoagulation should be considered in patients with two or more episodes of CVST and in those with one episode of CVST and ''severe'' hereditary thrombophilia [21].

This case is remarkable for its favorable and quick outcome and its rarity, because CSVT is an uncommon condition and heterozygous prothrombin G20210A genotype was only found predisposing factor for CSVT. Further studies of risk of recurrent venous thrombosis in patients with heterozygous prothrombin G20210A genotype with the larger sample size are required.

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