CASE REPORT

Cerebral venous thrombosis associated with thyrotoxicosis, the use of desmopressin and elevated factor VIII/von Willebrand factor

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SUMMARY

Cerebral venous thrombosis (CVT) is an uncommon disorder associated with diverse processes. We report a patient who, while receiving desmopressin and contraceptive pills (OCP), developed straight sinus thrombosis. Clinical assessment and laboratory investigations revealed untreated hyperthyroidism and a hypercoagulable state, characterised by high levels of von Willebrand factor, factor VIII coagulant activity and IgM cardiolipin antibody. The clinical picture improved with anticoagulation, treatment of hyperthyroidism and discontinuation of OCP and desmopressin. To the best of our knowledge, the association between the use of oral desmopressin and CVT has not been described. The multiple risk factors present in our case were probably additive in increasing the risk of CVT. Although this case represents a rare occurrence, practitioners should be alerted to the possible associations of desmopressin, oral contraceptives and Graves' disease with venous thrombosis.

BACKGROUND

Cerebral venous thrombosis (CVT) is an uncommon disorder. The clinical presentation may be confusing, but early diagnosis is important since the potential for recovery is improved provided therapeutic interventions occur promptly.¹ In the setting of an evolving subacute encephalopathy with headache, diencephalic and frontal signs and symptoms, MRI and magnetic resonance venography provide a rapid and non-invasive diagnosis of CVT. A number of conditions are associated with CVT, but to the best of our knowledge, its association with desmopressin and thyrotoxicosis has not been reported before.

CASE PRESENTATION

A 48-year-old woman experienced 2 days of headache, malaise and lethargy before developing stupor, vomiting, and bowel and bladder incontinence. History revealed 6 months of polyuria with occasional nocturnal incontinence treated with oral desmopressin (0.2 mg). Previous brain MRI (figures 1A and 2A), thyroid studies and antidiuretic hormone levels were normal. Other medical problems included asthma, gastro-oesophageal reflux disease and migraine. Her home medications included inhalers for asthma, lansoprazole and contraceptive pills (OCP). On admission, the pulse was 110 bpm, blood pressure was 149/80 and

temperature of 37.9°C which later increased to 40°C. Her general examination was unremarkable. On neurological examination, she was lethargic and disoriented with a flat affect. Speech was hypophonic and stuttering in character. Cranial nerves were normal except for absent venous pulsations. Motor examination showed fine bilateral postural and action tremor, increased tone on the right side, intact power, symmetrically brisk reflexes and bilateral Babinski signs. Cerebellar examination was normal, but gait was profoundly apraxic. Signs of meningeal irritation were absent.

INVESTIGATIONS

Admitting laboratory studies showed a leucocyte count of $11.8 \times 10^3/\text{mm}^3$ with neutrophil predominance, erythrocyte sedimentation rate of 40 and a normal chemistry profile. D-dimer was elevated (3.05 µg fibrinogen equivalent units/mL, reference <0.50). The electrocardiogram showed regular sinus rhythm without atrial fibrillation. Brain CT (figure 1B) revealed slight hypodensities in both thalami. Brain MRI (figure 1C) showed bilateral thalamic and left caudate hyperintensities with similar changes in both posterior frontal lobes. MR angiography of the head and neck was normal, while MR venogram showed thrombosis of the straight sinus and internal cerebral vein (figure 2B). An EEG revealed intermittent bifrontal slowing as well as independent left temporal slowing with several stereotyped sharp transients.

The patient's febrile state prompted an infectious workup that was unremarkable. This included negative blood and urine cultures. Cerebrospinal fluid studies were unrevealing with the exception of a mild lymphocytic-predominant pleocytosis (12/mm³; reference: 0–5) and protein elevation (137 mg/dL; reference: 15–60). Rheumatological workup revealed borderline elevated antinuclear antibodies (ANA) at 1:160 (normal 1:40), with a diffuse and speckled pattern. Rheumatoid factor was 35 IU/mL (normal <20) and perinuclear antineutrophil cytoplasmic antibody (p-ANCA) was 1:160 (normal is negative). Specific markers for aforementioned abnormal laboratory tests, including antidouble-stranded DNA (anti-ds-DNA), extractable nuclear antigen (anti-ENA) and antimyeloperoxidase antibodies, were negative. C3 level was normal, but C4 level was slightly decreased at 15 (normal 16–38 mg/dL). Hepatitis B and C serologies, in addition to anti-SSA/SSB, were also normal.

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Figure 1 (A) Baseline MRI axial T2 FLAIR sequence demonstrating no intracranial abnormalities. (B) Admission non-contrast axial CT head demonstrates bithalamic hypodensities. (C) Admission MRI axial T2 FLAIR reveals bilateral thalamic and left basal ganglia hyperintensities. (D) MRI axial T2 FLAIR sequence obtained 2 months after treatment demonstrating resolution of the bithalamic hyperintensities. FLAIR, fluid-attenuated inversion recovery.

Figure 2 (A) Baseline MRI sagittal T1 sequence with no evidence of intracranial abnormalities. (B) Admission MRI sagittal T1 sequence demonstrates abnormal signal in the straight sinus suggestive of venous thrombosis. (C) MRI sagittal T1 sequence obtained 2 months after treatment highlights resolution of abnormal signal in the straight sinus.

Thyroid workup was consistent with Graves' disease. This included a low thyroid-stimulating hormone ($<0.003 \mu\text{IU/mL}$; reference: $0.35\text{--}5.50 \mu\text{IU/mL}$), high T3 (329 ng/dL ; normal $60\text{--}181$), high free T4 (3.0 ng/dL ; normal $0.8\text{--}1.8$) and high thyroid-stimulating immunoglobulin (2.3 mg/dL ; normal <1.3). Other thyroid antibodies were negative and thyroid ultrasound was normal.

Haematological work up, including activated partial thromboplastin time, prothrombin time, thrombin time and dilute

Russell's viper venom time, was normal. Factor VIIIc, von Willebrand factor (vWF) antigen and ristocetin cofactor activity were elevated (446%, 350% and 405% of normal, respectively). Genetic analyses for factor V Leiden and the prothrombin 20210A polymorphism were negative. Flow cytometry for PI-linked antigen, used for screening and confirming the diagnosis of paroxysmal nocturnal haemoglobinuria, was also negative. Immunoglobulin G cardiolipin antibodies were absent; however, the IgM cardiolipin antibody titre was 1:512.

DIFFERENTIAL DIAGNOSIS

The other possibilities of diencephalic/bithalamic involvement, including 'top of the basilar artery' syndrome, hypertensive encephalopathy, Wernicke's encephalopathy, extrapontine myelinolysis, West Nile or Japanese encephalitis and Creutzfeldt-Jakob disease, were excluded based on the clinical presentation and appropriate diagnostic studies.

TREATMENT

Desmopressin and OCP were discontinued. The patient was anticoagulated with intravenous unfractionated heparin and subsequently transitioned to warfarin. Thyrotoxicosis was treated with propylthiouracil and propranolol.

OUTCOME AND FOLLOW-UP

Over the next 3 months, she improved substantially with minimal residual cognitive impairment, characterised by difficulty with concentration and information processing. Subsequent MRI/magnetic resonance venography (MRV) (figures 1D and 2C) showed complete patency of the venous sinuses and near-complete resolution of the high signal lesions. Her repeat factor VIII at 7 months follow-up, though improved, was still elevated at 201%. Convalescent levels of protein C, protein S, antithrombin (while off warfarin) and homocysteine were normal. Anticardiolipin antibody, ANCA and ANA resolved over time.

DISCUSSION

Subacute encephalopathy with increasingly severe headaches, followed by confusion, obtundation and vomiting, is a common presentation of deep CVT.¹ As expected from the anatomic territory served by the straight sinus/internal cerebral vein, the ischaemic areas included bilateral thalami, left caudate nucleus and patchy involvement of bilateral posterior frontal lobes. Her

primary symptoms of lethargy, thalamic aphasia (reduced spontaneous speech, preserved reading and stuttering repetitive speech), thalamic astasia (inability to stand despite normal strength) and neuropsychiatric signs (mood, affect and memory disturbances) reflected thalamic involvement. The right-sided extrapyramidal signs indicated left caudate nucleus involvement.

Although this is the first reported association of oral desmopressin with CVT, the authors recognise that several possible factors likely contributed to development of CVT in this patient (figure 3). First, OCP use is associated with increased risk of thrombotic events. A meta-analysis showed significant associations of the risk of venous thromboembolism in women using OCPs with deficiencies of antithrombin, protein C or protein S, or elevated levels of VIIIc, factor V Leiden and prothrombin G21210A.² Second, parenteral desmopressin has been associated with thrombotic events, related to increases in vWF and factor VIII.^{3–5} Third, thyrotoxicosis is also associated with elevated vWF and factor VIII.⁶ Fourth, elevated factor VIIIc is a recognised risk factor for deep venous thrombosis, and the persistent elevation in this patient after the acute phase, correction of thyrotoxicosis and discontinuation of desmopressin suggests a contributing role.^{7–9} Finally, the patient had a high-titre IgM cardiolipin antibody in an acute state, which subsequently resolved, suggesting an unlikely role.

The association between thyrotoxicosis and CVT is well recognised.⁶ Several mechanisms have been hypothesised to result in thrombosis with hyperthyroidism apart from its connection with atrial fibrillation and cardioembolic stroke. These include (1) hypercoagulability through influence of thyroid hormone on the coagulation-fibrinolytic system.¹⁰ Our patient had elevated factor VIII levels, which has also been rarely identified in other reports¹¹ and might be explained on the basis of increased sensitivity of factor VIII to catecholamines. If that

Figure 3 Several factors contributed to the development of hypercoagulable state characterised by elevated factor VIII/vWF levels and CVT in this patient. These include oral desmopressin, OCP, thyrotoxicosis and possibly anticardiolipin antibody. Details of these potential interactions are reviewed in the Discussion section. CVT, cerebral venous thrombosis; OCP, contraceptive pills; vWF, von Willebrand factor.

were the case, return to the euthyroid state would be accompanied by decline of factor VIII levels. (2) Stasis of venous blood flow and haemodynamic factors associated with large thyrotoxic goitre; this mechanism was not pertinent in this patient. (3) Abnormalities of the vessel wall, suggested by association of thyroid disorder with giant cell arteritis, based on the presence of giant cells in Graves' disease¹² and in Moyamoya disease. The progressive stenosis of the intracranial internal carotid arteries and their proximal branches could be explained by hyperactivity of cervical sympathetic nerves seen in thyrotoxicosis.¹³ These findings were not confirmed in large-scale studies, and as such, these associations are controversial.¹⁴

Another pertinent explanation of thyroid-associated autoimmune coagulation disorder in our patient was the presence of an IgM cardiolipin antibody. Antiphospholipid syndrome consists of certain clinical manifestations in the presence of persistent laboratory evidence of either antibodies against cardiolipin and/or a non-specific coagulation inhibitor dependent on phospholipid.¹⁵ Clinical manifestations can include thrombosis, thrombocytopenia, recurrent spontaneous abortions and livedo reticularis. Association of antiphospholipid antibodies and Graves' disease is limited to isolated case reports.^{16–17} Antiphospholipid antibodies cause a hypercoagulable state through interfering with the activity of a natural *in vivo* anticoagulant, β_2 -glycoprotein-I, which, through binding to negatively charged phospholipids, inhibits the contact activation of the intrinsic coagulation pathway.¹⁸ Association between antiphospholipid antibody syndrome and Graves' disease, which could have a genetic predisposition, suggested by the presence of the class HLA DR4 and DR7 antigens,¹⁹ can be explained by (1) cross-reactivity between β_2 -glycoprotein-I and thyrotropin receptor epitopes and (2) anti-TSH receptor antibodies can generate antibodies to epitopes of antiphospholipids.²⁰ It is interesting to speculate in our case that the cardiolipin antibody resolved with treatment of hyperthyroidism, suggesting a possible link. However, many authors believe that IgM cardiolipin antibodies are induced by exogenous factors (drugs and viral infections) and, as such, are not involved in the pathogenesis of venous thrombosis.²¹ Therefore, the resolution of cardiolipin antibodies and other autoimmune markers (ie, ANA and ANCA), following treatment of the hyperthyroid state in this patient, could represent an epiphenomenon and a non-specific marker of immune dysregulation.

Desmopressin, a vasopressin analogue, is a potent antidiuretic due to its high affinity to the V2 receptor. It has also been used in prevention and control of bleeding in von Willebrand disease, uraemia, cirrhosis and cardiac procedures. The use of desmopressin is associated with a low risk-to-benefit ratio, but the occurrence of thrombosis has been reported. Bond and Bevan³ described a patient with haemophilia A who developed post-operative myocardial infarction while receiving intravenous desmopressin and factor VIII concentrates. Pentimone and Del Corso⁴ described a case of venous thrombosis of the lower extremities and pulmonary embolus following desmopressin therapy for central diabetes insipidus. Neurological complications of desmopressin are mainly related to hyponatremia. Two cases of ischaemic stroke have been reported. The first involved a 93-year-old patient who developed a right frontoparietal stroke while receiving intravenous desmopressin for the management of uraemic bleeding.⁵ The second report described a case of intraoperative cerebral infarction after desmopressin administration for control of perioperative bleeding in an infant with end-stage renal disease and bilateral Wilms' tumour.²² As mentioned previously, to the best of our knowledge, the

association between the use of oral desmopressin and CVT has not been described.

The mechanism²³ by which desmopressin improves haemostasis and possibly promotes thrombosis remains only partially understood. The major effect likely results from increased levels of factor VIII and vWF. vWF has two major functions in haemostasis. First, it forms an adhesive bridge between platelets and the vascular subendothelial structures, as well as between adjacent platelets at sites of endothelial injury. Second, vWF is a carrier protein for factor VIII and prolongs its half life by protecting its proteolytic degradation in plasma. Hence, increase in factor VIII level is most likely secondary to vWF elevation. While a deficiency of vWF is responsible for a haemorrhagic diathesis (von Willebrand disease), there is increasing evidence that elevated vWF/VIII levels represent an important thrombotic risk factor including for CVT.²⁴ We hypothesise that these effects may have contributed to the development of CVT in our patient.

To support a causative role for a haematological abnormality identified after a cerebrovascular event, the abnormality should remain present in the following months or be present in family members. In our report, the persistent elevation of factor VIII several months after the acute phase, correction of thyrotoxicosis and discontinuation of desmopressin suggest a possible underlying haematological abnormality. Elevated plasma factor VIII coagulant activity (VIII: C) is now accepted as an independent marker of increased thrombotic risk. A plasma level of

Patient's perspective

- Cerebral venous thrombosis of straight sinus and internal cerebral vein: a patient's perspective.
- The most curious issue about damage to the thalamic area is the lack of memories. I was conscious during my acute hospitalisation, but have no memories of anything from the first 2 weeks (even no memory of two spinal taps, although I was fully awake for them).
- When I first became aware, it was overwhelming to try to assimilate all the information I received from family, friends and doctors, since it did not seem to relate to me. The return of my awareness seemed to be sudden and with no sense of missing anything. I was told I had held conversations with the doctors during this time, and that I talked coherently and intelligently, yet I have no memory of this.
- In the beginning, I was frustrated with the inability to access these memories, but I eventually realised that the thalamic damage meant my brain never created the memories in the first place.
- After those first few weeks, my recovery went quickly, as I pushed myself very hard physically and mentally. Since I am the primary breadwinner, I had to return to work as quickly as possible. My work involved literature research in the biomedical field, analysing literature and writing medical content for patient education materials, so I needed to come up to speed again intellectually. I went back to work full-time 5 months after the CVT. Residual deficits included brain fatigue (quite often in the first few years), and some decreased speed in information processing. However, I feel normal now and am still working—two jobs—one full-time and one part-time.

factor VIII over 150% has been considered a significant risk factor for deep vein thrombosis and a common prothrombotic risk factor for CVT by previous reports.^{7–9} The risk of thrombosis, as in this report, appears to be additive to that of OCPs, in contrast to the supra-additive risk observed for the hereditary thrombophilias.²⁵ Higher levels of factor VIII are heritable and thought to be related to reduce clearance from differential glycosylation of vWF by the ABO glycosylase.²⁶

Although the multiple risk factors in this patient precluded determination of any single aetiology, the challenging clinical picture revealed the necessity of exploring and appreciating the various potential pathophysiological mechanisms underlying CVT (figure 3). The combination of factors was probably cumulative in increasing the risk of CVT. Although this case represents a rare occurrence, practitioners should be alerted to the possible associations of oral contraceptives, Graves' disease and desmopressin therapy with cerebral venous sinus thrombosis.

Learning points

- ▶ Thrombotic complications have been reported in patients with hyperthyroidism through influence of thyroid hormone on the coagulation-fibrinolytic system.
- ▶ The role of increased factor VIII and von Willebrand factor (vWF) is increasingly recognised in thrombotic diseases, including CVT.
- ▶ The use of desmopressin is associated with a low risk-to-benefit ratio, but thrombosis related to increases in vWF and factor VIII has been reported.
- ▶ While there could be an association of antiphospholipid antibodies and Graves' disease, this could represent an epiphenomenon and a non-specific marker of immune dysregulation.

Competing interests None declared.

Patient consent Obtained.

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