CASE REPORT

Cerebral venous sinus thrombosis precipitated by Graves' disease

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Accepted 28 April 2018

SUMMARY

Cerebral venous sinus thrombosis usually occurs in patients with a precipitating condition such as thrombophilic disorders, pregnancy or due to medications, such as oestrogens. Some case reports have reported the co-occurrence of cerebral venous sinus thrombosis in patients with hyperthyroidism. However, the association of cerebral venous sinus thrombosis with hyperthyroidism remains contentious. We present the case of a patient who presented with a clinical picture of cerebral venous sinus thrombosis with no obvious precipitating factor. Further investigations revealed the presence of hyperthyroidism due to Graves' disease, which was thought to be the provocative disorder for cerebral venous sinus thrombosis. We would like to draw the attention of clinicians to a possible causative association between cerebral venous sinus thrombosis and hyperthyroidism.

BACKGROUND

Cerebral venous sinus thrombosis is an uncommon cause of stroke representing about 1% of all patients with strokes.¹ Cerebral venous sinus thrombosis occurs most commonly in young women, especially in those taking combined oral contraceptives, although it can occur in all age groups and in both sexes.² Most patients who develop cerebral venous sinus thrombosis have an underlying hypercoagulable state such as genetic pro-thrombotic conditions (anti-thrombin III deficiency, protein C deficiency, protein S deficiency, factor V Leiden mutation), nephrotic syndrome, inflammatory disorders (Behçet's disease, inflammatory bowel disease), haematological disorders (polycythaemia rubra vera, paroxysmal nocturnal haemoglobinuria, Waldenström macroglobulinemia), drugs (oral contraceptive pills, L-asparaginase), pregnancy and puerperium.³ Graves' disease is an autoimmune disease that involves the formation of stimulating antibodies against the thyrotropin receptor and results in clinical features of hyperthyroidism.⁴ Graves' disease has not been established as a risk factor for cerebral venous sinus thrombosis, although some case reports have suggested a possible association between these two conditions. We report the case of a patient who developed cerebral venous sinus thrombosis following a recent diagnosis of Graves' disease without any identifiable pro-thrombotic state.

CASE PRESENTATION

A 31-year-old man presented to the emergency department with a 4-day history of severe headache and projectile vomiting. He was diagnosed with Graves' disease 2 weeks prior to this presentation when he presented with palpitations and heat intolerance. His thyroid function tests were consistent with the diagnosis of hyperthyroidism and a pertechnetate thyroid scan revealed that the aetiology is Graves' disease. On physical examination, he was afebrile with a regular pulse rate of 110/min and blood pressure of 125/80 mm Hg. He was in distress due to pain and looked lethargic without confusion. He had no focal neurological deficits or signs of meningeal irritation. Ophthalmological examination was performed, which excluded the presence of papilloedema or visual field defects.

INVESTIGATIONS AND DIAGNOSIS

His laboratory investigations showed normal serum creatinine, urea, electrolytes, liver function tests and coagulation profile. His recent thyroid function tests showed a thyroid stimulating hormone level of <0.01 mIU/L (reference range: 0.45–4.5 mIU/L), free triiodothyronine level of 23.8 pmol/L (reference range: 2.6–5.7 pmol/L) and free thyroxine level of 30.5 pmol/L (reference range: 9–20 pmol/L). His Burch-Wartofsky score was calculated for the possibility of thyroid storm, which was 30 (see [table 1](#)). CT of the head with contrast revealed extensive thrombosis in the superior sagittal, straight and bilateral transverse sinuses ([figure 1](#)). MRI of brain with magnetic resonance venography confirmed the finding of cerebral venous sinus thrombosis involving the superior sagittal sinus, straight sinus and both transverse sinuses along with cerebral oedema of the left parietal lobe ([figure 2](#)).

TREATMENT

The management plan included intravenous hydration, anticoagulation using enoxaparin and warfarin and Lugol's iodine solution. Carbimazole and propranolol were continued. A comprehensive thrombophilia screen was ordered prior to starting anti-coagulation therapy. An extensive work-up for a possible underlying hypercoagulable state excluded the presence of protein C and protein S deficiency, hyperhomocysteinemia, factor V Leiden mutation, prothrombin gene mutation, anti-thrombin III deficiency, anti-phospholipid antibodies or anti-β₂-glycoprotein antibodies. Lupus

To cite: Rehman A, Husnain MG, Mushtaq K, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-224143

Table 1 Calculation of Burch-Wartofsky score* for our patient

Feature	Score
Temperature<37.7°C	5
Central nervous system dysfunction (mild)	10
Hepato-gastrointestinal dysfunction (none)	0
Pulse rate (90–109 beats/min)	5
Cardiovascular symptoms (none)	0
Arrhythmias (none)	0
Suggestive history (present)	10
Total score	30

Interpretation of score:>25 points, *possible* thyrotoxic storm; >45 points, *probable* thyrotoxic storm.

*Based on the Burch-Wartofsky scoring system as reported in ref.²³

anticoagulant antibodies were slightly elevated. Tests for antinuclear antibodies and antineutrophil cytoplasmic antibodies were negative. Serum complement levels were within normal limits. Activated partial thromboplastin time was low at 22 s (laboratory reference range: 25–33 s).

OUTCOME AND FOLLOW-UP

A follow-up magnetic resonance venography done at 3 months showed progressive recanalisation of dural venous sinuses and resolution of the cerebral oedema of the left parietal lobe. His thrombophilia screening was repeated twice, 6 months and 12 months after hospital discharge. Repeat lupus anticoagulant testing was negative on both these occasions. Warfarin therapy was stopped at 6 months. Radioactive iodine therapy was offered as a treatment for Graves' disease, but the patient declined and preferred to continue carbimazole. He remained asymptomatic at 18 months of follow-up and his thyroid function tests remained within normal limits.

DISCUSSION

Nearly 45 cases reported in the medical literature have suggested an association between hyperthyroidism and cerebral venous

sinus thrombosis (see table 2).^{5–9} Most cases have been reported in young or middle-aged patients with a predominance of women.⁵ In most of these cases, the underlying aetiology of hyperthyroidism was Graves' disease.^{6–7} These observations may be accounted for by the fact that Graves' disease is the most common cause of hyperthyroidism and affects women more than men. Hyperthyroidism has been associated with an increased risk of pro-thrombotic events.⁸ Observational studies have shown that venous thromboembolism and hyperthyroidism co-occur together more frequently than expected by chance alone.⁹ Previous data have shown that patients with hyperthyroidism often harbour a variety of abnormalities in the coagulation system with the most common being elevated levels of fibrinogen, factor VIII, factor IX and von Willebrand factor.¹⁰ A low activated partial thromboplastin time has been reported among patients with hyperthyroidism; the clinical significance of this finding remains uncertain.¹¹ Thyroid hormones can stimulate the synthesis of some coagulation factors such as factor VIII and fibrinogen.^{10 12 13} In addition, platelet activation induced by autoantibodies leading to thrombosis has been demonstrated in patients with Graves' disease.^{4 14 15} In a case-control study, Erem and colleagues showed that the mean platelet volume positively

Figure 1 CT venography of our patient demonstrating filling defects (arrowheads) in the (A) superior sagittal, (B) straight, (C) bilateral transverse and (D) left sigmoid sinuses suggestive of cerebral venous sinus thrombosis.

Figure 2 MRI of brain with magnetic resonance venography showing irregular filling defects (arrowheads) in the (A) superior sagittal, (B, C) straight sinus, both transverse sinuses, and (D) left sigmoid sinus with extension into the (E) left proximal internal jugular vein. (F) Localised cerebral oedema of the left parietal lobe (arrow) is also evident.

correlated with anti-thyroid peroxidase antibodies and free thyroxine level positively correlated with factor VIII activity.¹⁶ Graves' disease has also been hypothesised to cause endothelial dysfunction, which may alter the natural balance between pro-thrombotic and anti-thrombotic factors synthesised by the vascular endothelium.^{10 17} Burggraaf and co-workers reported that endothelial marker proteins (fibronectin, thrombomodulin, tissue plasminogen activator and von Willebrand factor) were elevated in patients with hyperthyroidism and that levels of these proteins directly correlated with elevated levels of circulating thyroid hormones.¹⁸ Further studies reported that endothelial dysfunction in hyperthyroidism leads to impaired synthesis of fibrinolytic proteins, thereby contributing to a pro-thrombotic state.¹⁹ Based on these observations, it seems biologically plausible that Graves' disease can increase the risk of cerebral venous sinus thrombosis.

Abnormalities of haemostatic mechanisms were evident in most previously reported cases of cerebral venous sinus thrombosis in patients diagnosed with hyperthyroidism.^{5 6} Mouton *et al* reported four cases of which all patients had elevated factor VIII levels and one patient also had activated protein C resistance.²⁰

Kim and his group reported four cases of venous thromboembolism among patients with hyperthyroidism and found that all patients had elevated levels of factor VIII.²¹ Knudsen-Baas *et al* reported the case of a 17-year-old girl with Graves' disease who developed cerebral venous sinus thrombosis and was found to be heterozygous for the MTFHR C667T gene mutation.⁶ Similarly, heterozygosity for factor V Leiden mutation was reported in a child with hyperthyroidism who developed cerebral venous sinus thrombosis.²² Our patient had no apparent abnormality detected in the coagulation panel and thrombophilia testing. Graves' disease appears to be the only likely factor that could have precipitated cerebral venous sinus thrombosis.

In view of the above discussion, a causal association between Graves' disease and cerebral venous sinus thrombosis seems probable. In more general terms, thyrotoxicosis (due to any cause) can induce a pro-thrombotic state, which may lead to thromboembolic phenomena.^{5 8 9} A whole body of evidence supports this observation and the present case provides further support for a causal role of Grave's disease in cerebral venous sinus thrombosis. Applying the Bradford-Hill criteria of causality to the association between thyrotoxicosis and cerebral venous

Table 2 Published cases suggesting an association between hyperthyroidism and cerebral venous sinus thrombosis

Citation	First author (year)	Cases
<i>Stroke</i> 1991; 22 (3):401–5	Schutta HS (1991)	1
<i>Stroke</i> 1995; 26 (3):496–7	Siebert CEH (1995)	2
<i>Postgrad Med J</i> 1996; 72 (848):355–68	Silburn PA (1996)	1
<i>Stroke</i> 1996; 27 (10):1731–3	Dulli DA (1996)	1
<i>Neth J Med</i> 1999; 55 (4):201–2	de Schryver EL (1999)	1
<i>Thyroid</i> 2000; 10 (7):607–10	Verberne HJ (2000)	1
<i>J Stroke Cerebrovasc Dis</i> 2000; 9 (2):89–90	Dai A (2000)	1
<i>Ann Saudi Med</i> 2000; 20 (1):29–31	Longe AC (2000)	2
<i>J Neurosurg</i> 2001; 94 (1):130–2	Ra CS (2001)	1
<i>J Neurol Neurosurg Psychiatry</i> 2002; 73 (4):458	Maes J (2002)	1
<i>Ir Med J</i> 2003; 96 (2):46–7	Molloy E (2003)	1
<i>Nippon Naika Gakkai Zasshi</i> 2003; 92 (10):2020–2	Morimoto S (2003)	1
<i>Endocr Pract</i> 2003; 9 (4):290–5	Colleran KM (2003)	1
<i>Rev Neurol</i> 2004; 39 (6):533–5	Madronero-Vuelta AB (2004)	1
<i>Rev Med Interne</i> 2004; 25 (12):920–3	Karouache A (2004)	2
<i>Eur Neurol</i> 2005; 54 (2):78–80	Mouton S (2005)	4
<i>Clin Res Cardiol</i> 2006; 95 (8):418–21	Werner D (2006)	1
<i>Rinsho Shinkeigaku</i> 2006; 46 (4):270–3	Kasuga K (2006)	1
<i>Blood Coagul Fibrinolysis</i> 2007; 18 (8):801–3	Squizzato A (2007)	1
<i>Brain Nerve</i> 2007; 59 (3):271–6	Nagumo K (2007)	1
<i>Eur J Intern Med</i> 2008; 19 (5):386–8	Romualdi E (2008)	1
<i>Intern Med</i> 2008; 47 (10):969–973	Makino M (2008)	1
<i>N Z Med J</i> 2008; 121 (1280):53–7	Kim D (2008)	4
<i>Am J Emerg Med</i> 2008; 26 (3):383.e1–2	Pekdemir M (2008)	1
<i>Neurol Sci</i> 2008; 29 (5):343–5	Strada L (2008)	1
<i>Appl Thromb Hemost</i> 2009; 15 (6):676–80	Danescu LG (2009)	1
<i>Thromb Res</i> 2011; 128 (1):98–100	Bensalah M (2011)	1
<i>Case Rep Neurol</i> 2011; 3 (3):203–9	Hermans E (2011)	1
<i>Pediatr Blood Cancer</i> 2012; 58 (1):107–8	van Eimeren VF (2012)	1
<i>J Cerebrovasc Endovasc Neurosurg</i> 2012; 14 (3):251–4	Hwang JU (2012)	1
<i>Endocrinol Nutr</i> 2012; 59 (7):462–3	Merino M (2012)	1
<i>Acta Neurol Belg</i> 2013; 113 (3):331–3	Migeot M (2013)	1
<i>BMJ Case Rep</i> 2013;bcr-2013-201130	Janovsky CCPS (2013)	1
<i>Intern Med</i> 2014; 4 (1):136	Knudsen-Baas KM (2014)	1
<i>Neurologist</i> 2015; 19 (2):53–5	Liu JC (2015)	1
<i>BMJ Case Rep</i> 2016;bcr2016216584	Waheed W (2016)	1
<i>Kosin Med J</i> 2017; 31 (2):179–83	Kim BR (2016)	1
<i>Am J Case Rep</i> 2017; 18 :194–7	Tanabe N (2017)	1

sinus thrombosis, temporality, plausibility and specificity were satisfied in this case. If previously published data are taken into account, coherence and consistency are also satisfied. As more research is published and more evidence is accumulated, the overall relationship between thyrotoxicosis and haemostatic factors will become clearer.

Learning points

- ▶ Hyperthyroidism can lead to enhanced activity of coagulation factors and impaired activity of fibrinolytic proteins.
- ▶ Patients with Graves' disease may have autoantibodies that lead to platelet activation.
- ▶ Hyperthyroidism, in general, and Graves' disease, in particular, can predispose to venous thromboembolism.
- ▶ Physicians should recognise hyperthyroidism as a risk factor for cerebral venous sinus thrombosis.

Contributors All authors were involved in direct care of the patient and conceived the idea of writing a case report. AR and MGH collected the data and

interpreted it, and wrote down the case presentation section of the manuscript. KM performed a literature review and wrote down the discussion section of the manuscript. MSE substantially reviewed the whole manuscript for important intellectual content. All authors read the manuscript and approved it for submission in its current form.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005;**352**:1791–8.
- 2 Coutinho JM, Ferro JM, Canhã P, et al. Cerebral venous and sinus thrombosis in women. *Stroke* 2009;**40**:2356–61.
- 3 Ferro JM, Canhã P, Stam J, et al. Prognosis of cerebral vein and dural sinus thrombosis. *Stroke* 2004;**35**:664–70.
- 4 Weetman AP, disease Graves'N *Engl J Med* 2000;**343**:1236–48.

- 5 Franchini M, Lippi G, Targher G. Hyperthyroidism and venous thrombosis: a casual or causal association? A systematic literature review. *Clin Appl Thromb Hemost* 2011;17:387–92.
- 6 Knudsen-Baas KM, Kråkenes J, Thordarson HB, et al. Cerebral venous thrombosis and hyperthyroidism. *Intern Med* 2014;4:1000136.
- 7 Molloy E, Cahill M, O'Hare JA, O'Hare JA. Cerebral venous sinus thrombosis precipitated by Graves' disease and Factor V Leiden mutation. *Ir Med J* 2003;96:46–7.
- 8 Squizzato A, Romualdi E, Büller HR, et al. Clinical review: Thyroid dysfunction and effects on coagulation and fibrinolysis: a systematic review. *J Clin Endocrinol Metab* 2007;92:2415–20.
- 9 Kootte RS, Stuijver DJ, Dekkers OM, et al. The incidence of venous thromboembolism in patients with overt hyperthyroidism. *Thromb Haemost* 2012;107:417–22.
- 10 Franchini M. Hemostatic changes in thyroid diseases. *Hematology* 2006;11:203–8.
- 11 Lippi G, Franchini M, Targher G, et al. Hyperthyroidism is associated with shortened APTT and increased fibrinogen values in a general population of unselected outpatients. *J Thromb Thrombolysis* 2009;28:362–5.
- 12 Franchini M, Montagnana M, Manzato F, et al. Thyroid dysfunction and hemostasis: an issue still unresolved. *Semin Thromb Hemost* 2009;35:288–94.
- 13 Chadarevian R, Jublanc C, Bruckert E, et al. Effect of levothyroxine replacement therapy on coagulation and fibrinolysis in severe hypothyroidism. *J Endocrinol Invest* 2005;28:398–404.
- 14 Lima CS, Zantut Wittmann DE, Castro V, et al. Pancytopenia in untreated patients with Graves' disease. *Thyroid* 2006;16:403–9.
- 15 Ligier S, Pham CD, Watters AK, et al. Purpura fulminans and anticardiolipin antibodies in a patient with Grave's disease. *Scand J Rheumatol* 2002;31:371–3.
- 16 Erem C, Ersoz HO, Karti SS, et al. Blood coagulation and fibrinolysis in patients with hyperthyroidism. *J Endocrinol Invest* 2002;25:345–50.
- 17 Cikim AS, Ofiaz H, Ozbey N, et al. Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. *Thyroid* 2004;14:605–9.
- 18 Burggraaf J, Lalezari S, Emeis JJ, et al. Endothelial function in patients with hyperthyroidism before and after treatment with propranolol and thiamazol. *Thyroid* 2001;11:153–60.
- 19 Li Y, Chen H, Tan J, et al. Impaired release of tissue plasminogen activator from the endothelium in Graves' disease - indicator of endothelial dysfunction and reduced fibrinolytic capacity. *Eur J Clin Invest* 1998;28:1050–4.
- 20 Mouton S, Nighoghossian N, Berruyer M, et al. Hyperthyroidism and cerebral venous thrombosis. *Eur Neurol* 2005;54:78–80.
- 21 Kim DD, Young S, Chunilal S, et al. Possible association of venous thromboembolism and hyperthyroidism: 4 case reports and literature review. *N Z Med J* 2008;121:53–7.
- 22 van Eimeren VF, Billingham L, Askalan R, et al. Cerebral sinus venous thrombosis in a child with hyperthyroidism. *Pediatr Blood Cancer* 2012;58:107–8.
- 23 Burch HB, Wartofsky L, thyrotoxicosis L-threatening, et al. *Endocrinol Metab Clin North Am* 1993;22:263–77.

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