Pearls & Oy-sters:

An uncommon initial presentation of thyrotoxicosis

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PEARLS

- Venous thrombosis is common in patients with thyrotoxicosis, with the cerebral venous system being frequently involved.
- Full anticoagulation with unfractionated heparin or low molecular weight heparin is the treatment of choice for cerebral venous sinus thrombosis (CVST), even for patients with hemorrhagic complications.
- Evaluation of thyroid function tests should be considered as a part of the diagnostic workup for patients who are diagnosed with CVST when its underlying etiology remains elusive.

OY-STERS

- Development of headache or focal neurologic deficits in a patient with thyrotoxicosis should prompt clinicians to evaluate for CVST.

CASE REPORT A 22-year-old man was brought to the emergency department by his family after he had 2 witnessed spells of involuntary, rhythmic movements of the right lower extremity that then generalized to the whole body. There were associated rhythmic eyelid and jaw movements. He had been drowsy for a few days prior and had been complaining of a constant holocranial headache that worsened when leaning forward. Other symptoms included hyporexia, cold sweats, subjective fevers, and diarrhea.

The patient had been diagnosed with Graves disease 1 year prior and started on methimazole. However, he had not taken it for the last 3 months. There was no history of seizures, head trauma, or CNS infections. There was no family history of seizures, although there were relatives with hypothyroidism.

On arrival, the patient was tachycardic, hypertensive, and diaphoretic. He was somnolent but easily arousable. There was no obvious papilledema on direct nondilated ophthalmoscopy. Cranial nerves were normal, and there were no focal motor or sensory deficits.

Thyroid-stimulating hormone (TSH) was undetectable and free T₄ was above the upper limit of detection. He was started on methimazole along with propranolol for thyrotoxicosis secondary to medication noncompliance. Given the recent events concerning for seizures, the patient was loaded with levetiracetam and placed on a maintenance dose.

CT of the head without contrast revealed a hyperdensity in the superior sagittal sinus (figure). MRI brain with and without gadolinium suggested a dural venous sinus thrombosis in the superior sagittal sinus and cortical swelling and vascular congestion in the left parietal region. The latter could be explained by impaired cortical venous drainage in this territory and would be consistent with the patient's seizure semiology involving the right lower extremity. Magnetic resonance venogram (MRV) with gadolinium confirmed extensive venous sinus thrombosis of the superior sagittal sinus (figure) as well as mild thrombosis of the right transverse and sigmoid sinuses. A routine 30-minute EEG performed interictally revealed diffusely slow background with no epileptiform discharges. Funduscopic examination performed at this time, 5 days after admission, showed interval development of bilateral grade 3 papilledema, likely secondary to increased intracranial pressure due to CVST.

A workup for hypercoagulability revealed elevated levels of factor VIII (>300%, with reference range 56%–91%). IV unfractionated heparin was started with aggressive hydration.

No further seizures were noted. Six days after admission, thyroid function tests were rechecked. TSH was still undetectable, but free T₄ had decreased to 3.5 ng/dL (reference range 0.8–17.7 ng/dL). The patient was discharged in stable condition on warfarin and was scheduled to follow-up in 3 months with a repeat MRV of the head. The importance of medication compliance was emphasized.

DISCUSSION CVST has an incidence of approximately 3–4 cases per million in adults and 7 cases per million in children.¹ The pathogenesis of CVST involves thrombosis of either cerebral veins or major

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(A) Hyperdensity on axial noncontrast CT (asterisk) and (B) filling defect on sagittal contrast-enhanced magnetic resonance venogram (arrows) confirm thrombus.

sinuses, both of which can lead to intracranial hypertension. Venous thrombosis can be promoted by 3 factors, which are referred to as the Virchow triad: hypercoagulability, stasis of blood flow, and abnormalities of the blood vessel wall. Some common clinical conditions that can predispose to CVST include hereditary thrombophilia, pregnancy and puerperium, postoperative states, intracranial or local infections, and use of oral contraceptive pills or other hormonal supplements. Approximately 25% of cases of CVST are considered to be idiopathic.²

The association between thyrotoxicosis and thrombosis was first described by Kaliebe in 1913.³ Since then, it has been noted that among patients with thyrotoxicosis and venous thrombosis, as many as 80% of thrombotic phenomena can occur in unusual locations, such as splanchnic veins and the cerebral venous system.⁴

The exact pathophysiologic mechanisms explaining the relation between thyrotoxicosis and thrombosis are not fully understood and there is insufficient evidence to demonstrate a strong causal relation between these 2 phenomena.^{4,5} However, it has been hypothesized that changes in the levels of thyroid hormones can lead to disequilibrium in the coagulation cascade. Hyperthyroidism can result in either increased synthesis or impaired clearance of multiple proteins that are mainly derived from the vascular endothelium, leading to elevated levels of molecules such as factor VIII, factor IX, von Willebrand factor, fibrinogen, fibronectin, and plasminogen activator inhibitor-1, therefore favoring a procoagulant state.^{4,6} Among these molecules, factor VIII has been more widely studied in thyrotoxicosis. Epinephrine infusions in healthy subjects are followed by increased factor VIII activity. Since hyperthyroid patients have increased sensitivity to the effects of catecholamines,

it is possible that in these cases even physiologic concentrations of epinephrine can enhance factor VIII activity. Similarly, normalization of factor VIII levels after euthyroid state is reached has been reported.⁷ Recently, a locus on chromosome 18 was identified near D18S53. This gene is involved in the pleiotropic modulation of factor VIII activity and activated protein C resistance, suggesting a link between these 2 variables and susceptibility to thrombosis.⁸ Finally, another contributing mechanism to the development of CVST in these patients could be compression of the axillary and subclavian veins resulting in venous stasis, which can be purely due to mass effect from an enlarged thyroid gland.⁹

Common manifestations of CVST include headache, vision problems, and focal neurologic deficits such as paresis or seizures. Seizures, which could be focal or generalized, occur in about 40% of patients, which is much more common than in patients with arterial infarcts. The highly variable clinical presentation of CVST sometimes leads to delays in diagnosis and treatment.¹

The most sensitive neuroimaging modality for CVST consists of MRI in combination with MRV.¹⁰ Rarely, if diagnosis is still uncertain, cerebral angiography may be needed. Initial treatment for CVST consists of anticoagulation with unfractionated heparin infusion or with low molecular weight heparin to arrest thrombosis and to prevent further elevations in intracranial pressure. Anticoagulation has been shown to be safe even in patients with hemorrhagic transformation secondary to CVST (Class IIa; Level of evidence B).¹⁰ Oral acetazolamide can be considered for treatment of intracranial hypertension (Class IIa; Level of evidence C).¹⁰ Other possible therapeutic options include endovascular thrombolysis or thrombectomy (Class IIa; Level of evidence

C).¹⁰ A case report of plasma exchange for the treatment of the CVST secondary to thyrotoxicosis has been published, but this treatment modality needs to be studied further.¹¹

The development of headache or focal neurologic deficits in a patient with thyrotoxicosis should prompt clinicians to evaluate for CVST. Similarly, although thyroid function can be abnormal in the setting of acute illness,¹² evaluation of thyroid function tests should be considered as a part of the diagnostic workup for patients who are diagnosed with CVST when its underlying etiology remains elusive.

AUTHOR CONTRIBUTIONS

Parneet K. Grewal: case concept and design, acquisition of data, interpretation of data, manuscript writing. Mauricio F. Villamar: case concept and design, acquisition of data, interpretation of data, manuscript writing. Flavius D. Raslau: neurodiagnostic evaluation, critical revision of manuscript for intellectual content. Michael R. Dobbs: case concept and design, interpretation of data, critical revision of manuscript for intellectual content.

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DISCLOSURE

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