Thyrotoxicosis and cerebral venous sinus thrombosis, causality or chance alone?☆

Tirotoxicosis y trombosis de senos venosos cerebrales, ¿causalidad o azar?

Cerebral sinus venous thrombosis is an uncommon cause of stroke. Three factors usually predispose to venous thrombosis: hypercoagulability states, venous stasis, and blood vessel wall changes.[1–3]

In patients with thyrotoxicosis, the increased activity of factor VIII,[4] amongst others, results in a hypercoagulability state and has been reported as being a factor which predisposes to cerebral sinus venous thrombosis. Cases reported in the literature suggest that the causative relationship between both is significantly higher than would be expected by chance alone.[5,6] A case illustrating this association is reported below.

A 30-year-old male with a history of migraine since 12 years of age who was being treated with tricyclic antidepressants attended the emergency room for migraine worsening over the previous week. He reported throbbing holocranial headache associated with photopsia, as well as paresthesia in the right half of the face and right upper limb. When questioned, the patient reported both a loss of approximately 8–10 kg in weight and hyperhydrosis over the previous year. A physical examination revealed bilateral grade II/IV papilledema at eye fundus, with no neurological focal signs. The examination was otherwise normal, with a heart rate of 80 beats per minute, and no fine distal tremor, exophthalmos, or goiter.

A supplemental complete blood count showed normal results, except for elevated fibrinogen levels (516.9 mg/dL; normal range, 200–400).

Thyroid function tests provided results consistent with hyperfunction: FT4 4.54 ng/dL (NR, 0.9–1.7), TSH 0.01 μU/mL (NR, 0.27–4.5), FT3 8.61 pg/mL (NR, 2–4.4).

Tests for autoimmunity markers (antinuclear, ANCA, anticardiolipin, antimitochondrial, antimicrosomal, anti-TSH receptor, and antithyroglobulin antibodies) were only positive for the latter, with values of 363 U/mL (NR, <280).

A hypercoagulability study showed a chromogenic factor VIII level > 120% (NR, 80–110) and a von Willebrand factor Ag level of 112% (NR, 80–110). No changes were found in any other proteins tested (antithrombin III, protein C, protein S, von Willebrand factor, A2-antiplasmin antibodies, plasminogen, and protein C resistance test).

Because of the findings of hyperthyroidism, thyroid gammagraphy was performed, which showed diffuse hyperplasia with increased uptake. MRI of the brain (Fig. 1), performed because of clinical signs of paresthesia, showed signal hyperintensity at the superior longitudinal sinus, the confluence of sinuses, the straight sinus, and the proximal portion of the transverse sinuses consistent with subacute dural sinus thrombosis.

Cerebral sinus venous thrombosis secondary to hyperthyroidism was suspected, and treatment was started with low molecular weight heparin and subsequently with coumarins, tapering corticosteroids, and low-dose thiamazole (5 mg/12 h).

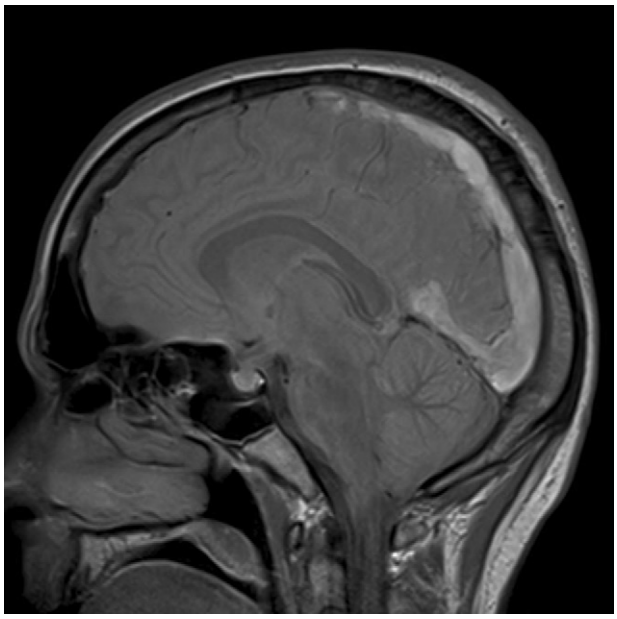

Figure 1 MRI of the brain showing signal hyperintensity of the superior longitudinal sinus, the straight sinus, and the proximal portion of the transverse sinuses.

After two weeks of treatment with thiamazole (10 mg/24 h), the patient was asymptomatic and showed subclinical hyperthyroidism: FT4 0.93 ng/dL (NR, 0.9–1.7), TSH 0.02 μU/mL (NR, 0.27–4.5), FT3 2.15 pg/mL (NR, 2–4.4); the dose was therefore decreased to 2.5 mg/24 h.

One month later, hormone values were within the normal range (FT4 0.98 ng/dL (NR, 0.9–1.7), TSH 0.81 μU/mL (NR, 0.27–4.5), FT3 2.99 pg/mL (NR, 2–4.4)), and antithyroid treatment was therefore discontinued.

The patient is currently asymptomatic and only receives oral anticoagulant therapy.

Although additional clinical trials are needed to confirm the association between coagulation/fibrinolysis disorders and thyroid function changes, the current evidence suggests that coagulation changes depend on the type of thyroid change. Patients with hypothyroidism usually appear to have an increased risk of bleeding, while hyperthyroid patients are more prone to arterial thrombosis.[6]

Several pathogenetic mechanisms predisposing hyperthyroid patients to a hypercoagulability state have been proposed, but the exact pathogenetic pathway is yet to be fully elucidated. Some of the changes found by different authors include increased plasma von Willebrand factor levels, improved platelet function, and increased factor II, VII, VIII, and X factors.[1,6,7]

The evidence reported for an association of hyperthyroidism and venous thrombosis is limited to a few case reports. According to a review by Franchini et al.[6] documenting 34 cases of venous thrombosis in patients with hyperthyroidism, thrombosis occurred in 80% of these patients in uncommon locations such as the splanchnic and, more frequently, the cerebral venous systems, which was the one involved in the reported patient. Subacute and

☆ Please cite this article as: Merino M, et al. Tirotoxicosis y trombosis de senos venosos cerebrales, ¿causalidad o azar? Endocrinol Nutr. 2012;59(7):462–3.

chronic venous thromboses were also more common than acute thrombosis.

Squizzato et al.[1] reported 13 cases of acute cerebral sinus venous thrombosis associated with thyroid disease. The most common etiology of hyperthyroidism was Graves–Basedow disease, and a hypercoagulability state and even vascular compression in the event of large goiter were suggested as a pathogenetic mechanism.

In the reported case, autoimmune hyperthyroidism could have been Hashimoto toxicosis instead of Graves–Basedow disease. Both of them may show diffuse hyperuptake at gammagraphy, but the absence of positive TSH receptor antibodies and the good response to antithyroid treatment suggest Hashimoto toxicosis as the first possibility, despite the fact that 10% of patients with Graves–Basedow disease test negative for these antibodies.

Thus, although there are many risk factors for the development of cerebral sinus venous thrombosis, such as hereditary thrombophilia, oral contraceptives, pregnancy, and postpartum, hyperthyroidism should always be considered.[1,6,8] In patients with hyperthyroidism and neurological symptoms, the diagnosis of cerebral sinus venous thrombosis should also be suspected and coagulation tests should be performed.

If this potential causal relationship is supported by larger observational studies, this may have significant clinical implications, particularly for prevention and treatment.

References

1. Squizzato A, Gerdes VEA, Brandjes DPM, Büller HR, Stam J. Thyroid diseases and cerebrovascular disease. Stroke. 2005;36:2302–10.
2. Siegert CEH, Smelt AHM, De Bruin TWA. Superior sagittal sinus thrombosis and thyrotoxicosis. Possible association in two cases. Stroke. 1995;26:496–7.
3. Verberne HJ, Fliers E, Prummel FM, Stam J, Brandjes PD, Wiersinga WM. Thyrotoxicosis as a predisposing factor for cerebral venous thrombosis. Thyroid. 2000;10:607–10.
4. Mouton S, Nighoghossian N, Berruyer M, Derex L, Philippeau F, Cakmak S, et al. Hyperthyroidism and cerebral venous thrombosis. Eur Neurol. 2005;54:78–80.
5. Strada L, Gandolfo C, Del Sette M. Cerebral sinus venous thrombosis in a subject with thyrotoxicosis and MTHFR gene polymorphism. Neurol Sci. 2008;29:343–5.
6. 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.
7. Usami K, Kinoshita T, Tokumoto K, Ino T, Ozawa K, Kimura T, et al. Successful treatment of plasma exchange for severe cerebral venous thrombosis with thyrotoxicosis. J Stroke Cerebrovasc Dis. 2009;18:239–43.
8. Lodha A, Haran M, Frankel R, Shani J. Thyrotoxicosis causing arterial and venous thrombosis. Am J Med Sci. 2009;338:428.

María Merino[a,*], María Guadalupe Guijarro[a], Paloma Iglesias[a], Yolanda Aladro[b], Paloma Montero[b]

[a] *Servicio de Endocrinología y Nutrición, Hospital Universitario de Getafe, Getafe, Madrid, Spain*
[b] *Servicio de Neurología, Hospital Universitario de Getafe, Getafe, Madrid, Spain*

* Corresponding author.
E-mail address: marietta84@hotmail.com (M. Merino).

Severe hypomagnesemia refractory to oral supplementation associated to omeprazole treatment☆

Hipomagnesemia severa refractaria a la suplementación oral asociada al tratamiento con omeprazol

Since the initial article by Epstein in 2006,[1] several reports have highlighted the relationship between long-term treatment with proton pump inhibitors (PPIs) and hypomagnesemia. Although very few cases have been reported to date, this may be an adverse effect more common than expected because of the high number of patients who receive this treatment. We report the case of a patient with hypomagnesemia refractory to treatment with oral supplementation that resolved upon discontinuation of omeprazole treatment.

A 65-year-old male patient was admitted after experiencing an episode of generalized tonic-clonic seizures. His personal history included HBP treated with doxazosin and valsartan/hydrochlorothiazide, cryptogenic focal epilepsy diagnosed in 2005 treated with levetirazetam, and atrial flutter (on anticoagulation with warfarin). He had had gastroesophageal reflux, which was being treated with omeprazole 20 mg, for 20 years.

Significantly decreased plasma calcium magnesium, and potassium levels were found upon admission, and treatment with intravenous and subsequently oral magnesium supplements was therefore started. On the first three days, calcium and potassium supplements were also given. Magnesium levels normalized with intravenous supplementation, but gradually decreased later to plasma levels similar to baseline values despite high oral supplementation (Table 1). Urinary magnesium losses were very low, which suggested that hypomagnesemia was related to deficient absorption. The patient reported a balanced diet and no alcohol or laxative use. Celiac disease and pancreatic insufficiency were ruled out. An attempt was made to substitute magnesium pidolate for lactate, but it was discontinued due to intolerance. Hydrochlorothiazide treatment was also discontinued with no improvement in laboratory results.

☆ Please cite this article as: Martínez Faedo C, et al. Hipomagnesemia severa refractaria a la suplementación oral asociada al tratamiento con omeprazol. Endocrinol Nutr. 2012;59(7):463–5.