Case Report

# Stroke in Thrombotic Thrombocytopenic Purpura Induced by Thyrotoxicosis: A Case Report

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> Thrombotic thrombocytopenic purpura (TTP) is a hematologic disease involving the platelet aggregation and resulting in hemolytic anemia, thrombocytopenia, and microvascular occlusion. Although frequent neurologic features are headache and confusion, focal deficit is described in 30% of the cases. There are a lot of causes inducing thrombotic thrombocytopenic, but reports are lacking when associated with Grave disease. We describe the case of a 51-year-old Caucasian woman presenting a 24-hour story of sudden onset of dysarthria and left superior limb palsy. Four months before, she developed severe hyperthyroidism associated with petechiae, hemolytic anemia, thrombocytopenia, and schistocytes at blood film examination. Relapse of TTP in association with Grave disease was diagnosed. There are few reports describing association between Grave disease and TTP with only mild neurologic involvement. We described, to our knowledge, the first case of acute ischemic stroke secondary to thrombotic thrombocytopenic induced by thyrotoxicosis. Key Words: Stroke-cerebrovascular diseasethrombotic angiopathy-hyperthyroidism-hematologic disease-steroids. © 2014 by National Stroke Association

# Introduction

Thrombotic thrombocytopenic purpura (TTP) is a hematologic disease, involving the platelet aggregation and resulting in microangiopathic hemolytic anemia, thrombocytopenia, and microvascular occlusion. Most frequent neurologic features are headache and confusion. Focal deficit is described in 30% of the cases.

The pathway involved in TTP is a deficient activity because of hereditary or acquired deficiency of A disinte-

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grin and mettaloprotease with thrombospondin type 1 (ADAMTS-13), a plasma metalloprotease cleaving large multimers of Von Willebrand factor released by the endothelium. Most cases are acquired with specific antibodies targeting ADAMTS-13.<sup>1,2</sup> In this condition, these altered multimers conduct to platelet thrombi formation in microcirculation, leading to hypoxemia, broken erythrocytes (called schistocytes), and thrombocytopenia.

Several autoimmune conditions have been associated with TTP, but reports are lacking for the association between Grave disease and TTP. We described, to our knowledge, the first case of acute ischemic stroke secondary to TTP induced by thyrotoxicosis.

#### Case Report

We describe the case of a 51-year-old Caucasian woman presenting a 24-hour story of sudden onset of dysarthria and left superior limb palsy.

Four months before, she developed severe hyperthyroidism associated with petechiae on her upper arms.

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Hemolytic anemia, thrombocytopenia, and schistocytes at blood film examination were found. TTP associated with Grave disease was diagnosed and plasmapheresis performed. Hyperthyroidism was treated with corticosteroid (methylprednisolone 1 mg/kg) and beta-blockers (bisoprolol 2.5 mg/d). She had a full progressive recovery with free T4 normalized 4 days after admission, normal platelet count 7 days after admission, and normal thyroid stimulating hormone (TSH) 3 weeks after admission. Low ADAMTS-13 activity (<3%, N > 40%) with positive test

On the day of admission, neurologic examination showed mild left superior limb palsy and left inferior facial palsy causing paretic dysarthria. Bipyramidal syndrome with bilateral achilles clonus and bilateral Babinsky were also found.

for specific inhibitor was demonstrated.

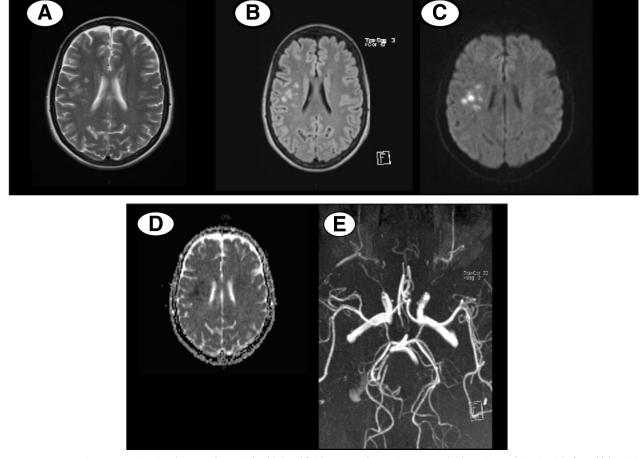
Biological findings showed mild hemolytic anemia (hemoglobin: 10 g/dL; normal: 13.5-17.5 g/dL), mild thrombocytopenia (platelet count: 120,000/ $\mu$ L; normal: 160,000-400,000/ $\mu$ L), and schistocytes at blood film examination. Thyroid test showed TSH < .01  $\mu$ U/mg (normal: .2-4  $\mu$ U/mg) with T4 at 77.7 pg/mL (normal: 10-19.5 pg/

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mL). Alpha-2-hapto was low, 33.2 mg/dL (normal: 50-190 mg/dL). Lactate deshydrogenase and bilirubin were normal. A magnetic resonance imaging (Fig 1) showed an acute ischemic stroke in superficial territory of the right middle cerebral artery. We also observed a decreased number of collaterals from the right middle cerebral artery compared with the left side.

Classic cardiovascular evaluation, including transthoracic and transoesophageal cardiac ultrasonography, 24 hours of cardiac rhythm recording, supra-aortic arteries ultrasonography, and magnetic resonance angiography were all negative and allowed us to exclude another cause of stroke. Laboratory and autoimmune tests for thrombophilia were negative. There were no diabetes mellitus, dyslipidemia or familial history of stroke, or any other cardiovascular events. Blood pressure was normal at admission. In these conditions, relapse of TTP in association with reactivation of Grave disease was the only plausible etiology for the stroke.

A 10-day therapy with 1 mg/kg of methylprednisolone was started to control thyroid function, but we did not reach any beneficial effect. Then, 10 mCi of I-131 followed



**Figure 1.** Magnetic resonance imaging shows axial T2-weighted (A) and fluid-attenuated inversion recovery (B) hyperintense lesion in right frontal lobe. Axial diffusion-weighted imaging (C) and apparent diffusion coefficient (D) shows us acute ischemic lesion in this area. Maximum intensity projection sequences (E) show reduced branches from right middle cerebral artery compared with the left side.

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by maintaining therapy by Lugol and methylprednisolone allowed an improvement of hyperthyroidism. Platelet count and hemoglobin became normal, and no more schistocytes were observed. Alpha-2-hapto returned to normal values. Six weeks later, our patient benefited of total thyroidectomy, and no relapse of TTP is noticed after 6 months of follow-up.

### Discussion

TTP is associated with several conditions, including autoimmune disorders like autoimmune hemolytic anemia,3 systemic lupus erythematosus,<sup>4</sup> Sjogren syndrome,<sup>5</sup> or systemic sclerosis.<sup>6</sup> There are few reports describing the association between Grave disease and TTP. Neurologic involvement was mild in these cases, with headache,<sup>7</sup> confusion, and disorientation.<sup>8,9</sup> To our knowledge, severe brain involvement by TTP in addition to Grave disease has never been reported. On the other hand, association between idiopathic thrombocytopenic purpura and Grave disease is well demonstrated.<sup>10</sup> With this fourth description of concomitant TTP and Grave disease, we hypothesize that hyperthyroidism triggers autoimmune mechanisms leading to TTP. The improvement at the same time of Grave disease and TTP with antithyroid therapies could support this hypothesis.

Plasma exchange is the best therapy for TTP. High dose of steroids should be considered at the onset of treatment. Antiaggregation has not been proved efficient, but because of its safety, aspirin could be given when platelet count is more than 50,000/µL.<sup>11</sup> It is suggested that antithyroid therapies could improve idiopathic thrombocytopenic purpura, but there is no data about a response of TTP to improvement of hyperthyroidism.<sup>12</sup> At relapse, our patient was treated only with antithyroid therapies and methylprednisolone. Then we noticed an improvement of the thrombotic microangiopathy at the same time as thyroid function tests, which suggests that TTP is caused by several autoimmune disorders induced by hyperthyroidism. In this case, the favorable outcome allows us to avoid a treatment by plasmapheresis. Nevertheless, total plasma exchange and high dose of corticosteroids remain first-line treatment for TTP if available.<sup>13</sup>

In conclusion, the arousal of stroke in a Grave patient implies looking for thyrotoxicosis, hemolytic anemia, and thrombocytopenia because of the specific treatment of TTP.

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