

Fatal ischemic stroke in a case of progressive moyamoya vasculopathy associated with uncontrolled thyrotoxicosis

Bon D. Ku¹, Key-Chung Park², and Sung Sang Yoon²

¹Department of Neurology,
International St. Mary's Hospital,
Catholic Kwandong University
College of Medicine, Incheon;

²Department of Neurology, Kyung
Hee University School of Medicine,
Seoul, Korea

To the Editor,

Several studies have described strokes that were associated with thyrotoxic moyamoya vasculopathy [1-5]. Although a majority of these cases followed a benign disease course in a euthyroid state after the stroke, this report describes a case of fatal ischemic stroke in a patient with progressive moyamoya vasculopathy associated with uncontrolled thyrotoxicosis.

A 42-year-old woman visited the emergency room complaining of left-handed clumsiness, palpitations, and dyspnea. Her medical history was unremarkable, but a physical examination revealed mild bilateral lid retraction with slight exophthalmos, warm moist skin, and a diffuse goiter that was approximately twice the normal size. A neurological examination showed mild left-handed clumsiness and fine tremors in both hands. Laboratory examinations including lupus anticoagulant, anticardiolipin antibody, antinuclear antibody, and homocysteine tests and thrombotic disorder and lipid profiles were unremarkable. However, the patient's thyroid function findings were abnormal and compatible with thyrotoxicosis, with a tri-iodothyronine (T₃) of 5.5 g/dL, thyroxine (T₄) of 14.0 g/dL, and thyroid-stimulating hormone (TSH) < 0.03 IU/mL.

Brain magnetic resonance imaging (MRI) revealed several small ischemic lesions in the bilateral basal ganglia and periventricular white matter. Conventional cerebral angiography showed total occlusion of the right supraclinoid internal carotid artery (ICA) with fine reticular collateral vessels, as well as severe stenosis in the proximal left middle cerebral artery (MCA) and proximal anterior cerebral artery (ACA), with numerous leptomeningeal collateral networks. There was also a slightly delayed transit time, incomplete visualization of the distal cortical branches, and prominent collateral vessels emerging from both posterior cerebral arteries (Fig. 1). Encephaloduroarterio-synangiosis (EDAS) was performed on the right side, but the patient's antithyroid drug compliance was very poor.

One year later, the patient revisited the emergency room due to fever, confusion, right-sided weakness, and emotional upset after a quarrel with her husband. On arrival, a blood gas analysis revealed respiratory alkalosis due to hyperventilation (pH 7.61, pCO₂ 21 mmHg, pO₂ 115.8 mmHg, and HCO₃ 38 mmol/L) and follow-up brain MRI revealed a small acute infarction in the left caudate and progression of the ischemic lesions in the bilateral basal ganglia and periventricular white

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Correspondence to Bon D. Ku, M.D.

Department of Neurology,
International St. Mary's Hospital,
Catholic Kwandong University
College of Medicine, 25 Simgok-ro
100beon-gil, Seo-gu, Incheon
404-834, Korea
Tel: +82-32-290-2914
Fax: +82-32-290-3879
E-mail: bondku34@cku.ac.kr

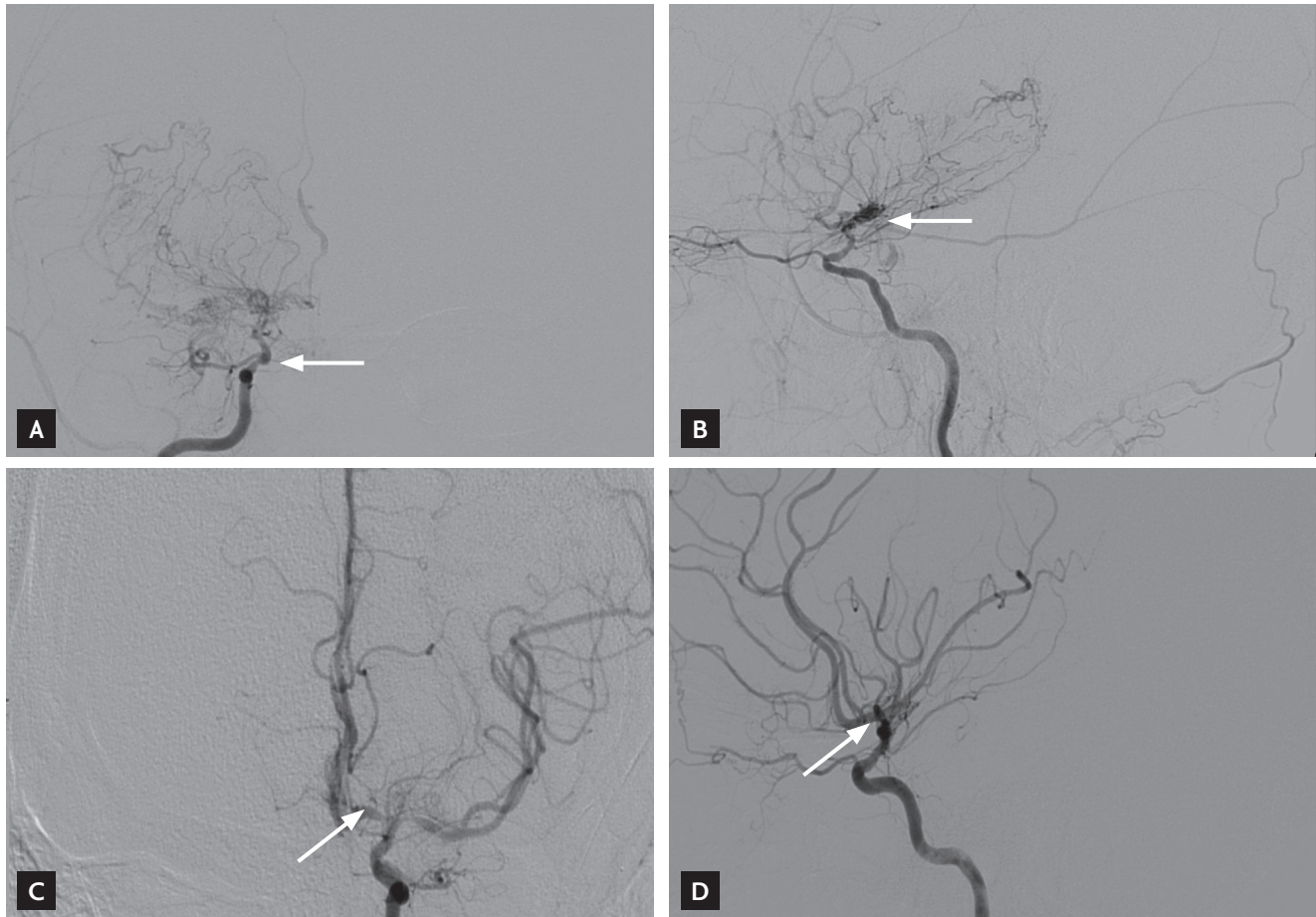


Figure 1. A conventional cerebral angiography of the patient showed total occlusion of the right supraclinoid internal carotid artery (ICA) with fine reticular collateral vessels (A, B; arrows) and severe stenosis in proximal portion of left middle cerebral and anterior cerebral arteries bifurcation site in left ICA (C, D; arrows).

matter. Thyroid function testing showed aggravated thyrotoxicosis that was compatible with thyrotoxic crisis, with a T_3 of 7.5 g/dL, T_4 of 18.0 g/dL, TSH < 0.03 IU/mL, thyroglobulin antibody of 871.5 U/mL, antimicrosomal antibody of 2,850 U/mL, thyroglobulin antigen of 64.5 ng/mL, and TSH receptor antibody of 492.1%. Follow-up cerebral angiography showed decreased fine reticular collateral vessels in the right ICA and progressive stenosis in the proximal left MCA and ACA, with poor leptomeningeal collaterals (Fig. 2).

After treatment for a thyroid storm, EDAS was considered on the left side. While treating the thyrotoxicosis, the patient complained of recurrent chest tightness and dyspnea, which was followed by hyperventilation that resulted in right-sided numbness and clumsiness. Before her 11st admission, the patient had quarreled

with her husband and complained of dyspnea and palpitations followed by hyperventilation. At this time, her blood gas analysis with oxygen administration revealed severe respiratory alkalosis (pH 7.63, pCO_2 19 mmHg, pO_2 121.6 mmHg, and HCO_3 36 mmol/L). Following this hyperventilation episode, the patient was irritable, her mental status decreased gradually, and she subsequently began to develop sweating, tremulous movements of the entire extremities, and generalized tonic-clonic seizures. Her condition deteriorated rapidly over the next 3 days and she exhibited intermittent respiratory holding with irregular tachyarrhythmia. Follow-up brain imaging revealed multiple large infarctions in the hemisphere with progressive left subfalcine herniation. The patient's thyrotoxicosis remained uncontrolled following the stroke and she died of cerebral herniation 17

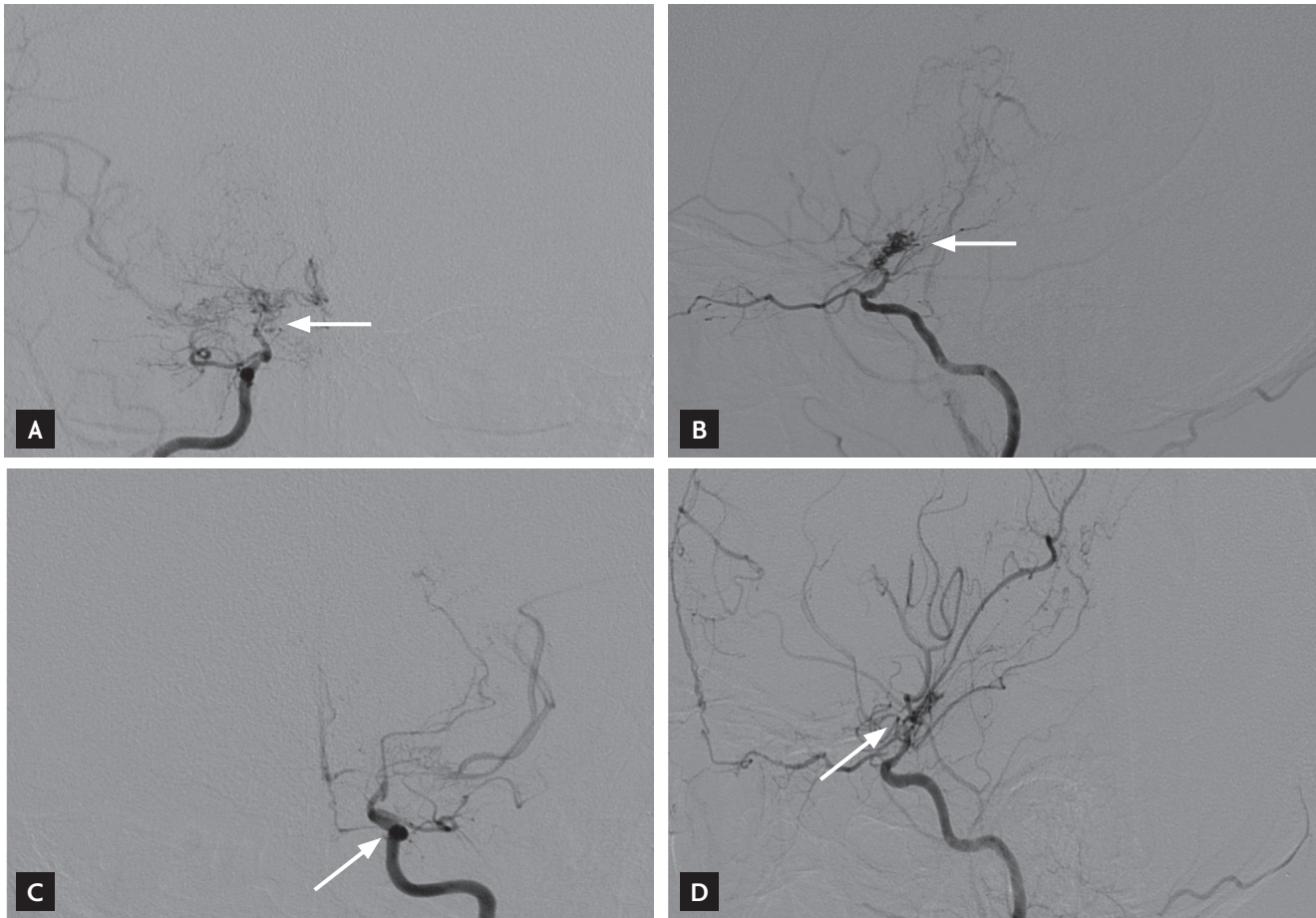


Figure 2. The follow-up cerebral angiography showed decreased fine reticular collateral vessels in right internal carotid artery (ICA) (A, B; arrows) and progressive stenosis in proximal portion of middle cerebral artery and anterior cerebral artery bifurcation site in left ICA with decreased reticular collaterals (C, D; arrows).

days after her admission.

A literature review identified eight selected published cases, including the present case, of moyamoya disease or its variants with Graves disease (Table 1) [1-5]. Except for one, all of the patients were female and a majority of the patients were Asian, particularly Japanese. Most cases were young adults (16 to 40 years of age), except for two children [1], and most showed a benign clinical course, except for one case with fulminant bihemispheric infarction [2]. A fulminant stroke occurred in the presence of uncontrolled thyrotoxicosis only in the report by Hsu et al. [2] and the present case.

The exact mechanisms underlying the association between progressive moyamoya vasculopathy and thyrotoxicosis remain unclear, but the hyperactivity of the cervical sympathetic nerves that results from

thyrotoxicosis may contribute to the progressive cerebral artery occlusion [3]. Furthermore, thyrotoxicosis may influence pathological vascular changes and the cerebral hemodynamics of moyamoya vasculopathy via autoimmune mechanisms and the cross-reactivity of TSH receptor antibodies with antigens derived from cerebral arteries can result in autoimmune-mediated vasculitis [3]. The deposition of autoimmune antibodies or immune complexes is the most probable trigger factor in the sequential cascade by which growth factors stimulate angiogenesis [4]. The direct toxic effects of excessive thyroid hormone levels may also contribute to dilated cardiomyopathy via increased cardiac muscle sensitivity [2,3]. It is also possible that moyamoya disease and Graves disease are both the result of T-cell dysregulation [1,3], but a common pathogenic linkage

Table 1. Summary of the published cases of moyamoya thyrotoxicosis

| Study | Sex/age | Race | Symptom | Imaging | Angiogram | Treatment | Outcome |
|--------------------------|---------|-----------|---------------|------------|-----------|-----------|-----------|
| Im et al. (2005) [4] | F/22 | Korean | Visual defect | Infarction | MD | AM/BS | Recovered |
| | F/22 | Korean | Hemiparesis | Infarction | MD | AM/BS | Recovered |
| | F/22 | Korean | Hemiparesis | Infarction | MD | AM/BS | Recovered |
| | F/25 | Korean | Hemiparesis | Infarction | MD | AM/BS | Recovered |
| Hsu et al. (2006) [2] | F/40 | Caucasian | Hemiparesis | Infarction | MD | AM | Died |
| Golomb et al. (2005) [1] | F/10 | Caucasian | Hemiparesis | Infarction | MD | AM | Recovered |
| Shen et al. (2006) [3] | F/23 | Chinese | Hemiparesis | Infarction | MD | AM | Recovered |
| Present study | F/42 | Korean | Clumsiness | Infarction | MD | AM/BS | Died |

MD, moyamoya disease; AM, anti-thyroid medication; BS, bypass surgery.

between T-cell dysregulation and moyamoya thyrotoxicosis remains to be proven.

In this case, the patient's thyrotoxicosis may have triggered cellular proliferation and vascular change. Utku et al. [5] reported the occurrence of reversible magnetic resonance angiographic findings in a patient with autoimmune Graves disease in conjunction with well-controlled thyroid hormone levels. In that patient, long-term uncontrolled thyrotoxicosis played a role in the manifestation of aggravated abnormal cerebral vessels in the terminal portion of the ICA. It has also been established that perioperative thyroid hormone levels have an important influence on surgery-related cerebral ischemic injury in patients with thyrotoxic moyamoya vasculopathy [3].

The ictus in the present case was thought to be induced by the patient's hyperventilation, which has not been described previously. It is unclear whether hyperventilation was the primary cause of the patient's fatal stroke, but it is possible that hyperventilation-induced vasoconstriction of the leptomeningeal collateral vessels changed the patient's critical area into a symptomatic ischemic zone.

In conclusion, although it is unclear whether thyrotoxicosis and moyamoya vasculopathy share common immunological processes or this case is a simple epiphenomenon, the regulation of thyrotoxicosis and the avoidance of hyperventilation are extremely important when these diseases are comorbid.

Keywords: Moyamoya disease; Thyrotoxicosis

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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