Acute Thyrotoxicosis of Graves Disease Associated with Moyamoya Vasculopathy and Stroke in Latin American Women: A Case Series and Review of the Literature

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■ OBJECTIVE: **Moyamoya disease is a cerebral vasculopathy characterized by stenosis of the terminal internal carotid artery, proximal middle cerebral artery, and anterior cerebral artery. There is an association between moyamoya vasculopathy and Graves disease, primarily in Asian populations. Here, we present the largest series of non-Asian, predominantly Latino patients with moyamoya vasculopathy in the setting of Graves thyrotoxicosis, as well as the largest review of the literature to date.**

■ METHODS: **We retrospectively analyzed patients presenting with stroke in the setting of clinical Graves disease to our institution from 2004 to 2014. Moyamoya vasculopathy was diagnosed by magnetic resonance angiography in all patients.**

■ RESULTS: **Eight patients with Graves disease thyrotoxicosis and moyamoya vasculopathy were identified. Six patients were effectively managed with aggressive medical management using antithyroid and antiplatelet medications. No recurrent strokes were noted once thyrotoxicosis was controlled. Intracranial bypass was necessary in 2 patients who failed medical management. Seventy-nine additional cases were reported from the literature. There was no significant difference in clinical improvement between medical therapy alone and medical therapy with neurosurgical prophylaxis (87.0% vs. 88.0%, respectively; $P = 0.94$).**

■ CONCLUSIONS: **Moyamoya vasculopathy associated with Graves disease thyrotoxicosis in non-Asian women may be more common than previously thought. In addition, our series suggests that thyrotoxicosis promotes the progression of vasculopathy. Based on our review, there is no significant difference in clinical improvement between proper medical and surgical therapies. Aggressive medical therapy should be considered first-line treatment for moyamoya vasculopathy with Graves thyrotoxicosis, with neurosurgical rescue reserved for medically refractory cases.**

INTRODUCTION

Moyamoya disease (MMD) is an idiopathic chronic, occlusive bilateral cerebral vasculopathy first described by Takeuchi and Shimizu in 1957.[1] Moyamoya syndrome is a unilateral or bilateral vasculopathy with a known association.[2] Both are characterized by angiographic stenosis of the terminal portion of the internal carotid arteries (ICAs), proximal portions of the anterior cerebral arteries (ACAs), and middle cerebral artery (MCA) with the development of a thin collateral network of small vessels that has an appearance similar to a puff of smoke, from which the disease derives its Japanese name.[3,4] A moyamoya vasculopathy has been described

Key words
- Graves disease
- Moyamoya
- Stroke
- Vasculopathy

Abbreviations and Acronyms
ACA: Anterior cerebral artery
EC-IC bypass: Extracranial-intracranial bypass
GD: Graves disease
ICA: Internal carotid artery
ICD-9: *International Classification of Diseases, Ninth Revision*
MCA: Middle cerebral artery
MMD: Moyamoya disease
MRA: Magnetic resonance angiography
mRS: Modifeid Rankin Scale
PCA: Posterior cerebral artery
STA: Superficial temporal artery
TSH: Thyroid-stimulating hormone

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in association with several conditions, including Graves disease (GD) thyrotoxicosis.[5]

GD is an autoimmune hyperthyroid state in which there are autoantibodies to the thyroid-stimulating hormone receptor, thyroid peroxidase, or thyroglobulin. There have been fewer than 100 cases, mostly of Asian women, in whom a moyamoya vasculopathy associated with GD has been described.[6-9] The natural history and risk of these associations are still unclear, and the duration of hyperthyroidism necessary to develop vasculopathy has not been reported. The association of increased thyroid antibodies with moyamoya vasculopathy in GD has been reported previously in Asian patients.[4,10] Recently, the presence of increased thyroid antibodies with intracranial stenosis in young patients without GD has been reported.[11] In addition, because of the limited number of cases, formal guidelines do not exist for the treatment of GD with moyamoya vasculopathy.

Here, we present the largest series of non-Asian, predominantly Hispanic/Latin American, patients presenting with a moyamoya vasculopathy in the setting of uncontrolled Graves thyrotoxicosis and our experience with medical and surgical management. We have also conducted a systematic review of the current literature to give insights into the effectiveness of the various treatment approaches for moyamoya vasculopathy with concurrent GD.

METHODS

We retrospectively analyzed patients presenting with ischemic strokes in the setting of clinical GD to our institution from 2004 to 2014. Institutional review board approval per institutional criteria for stroke registry was obtained.

In a retrospective stroke registry review of principal diagnoses with *International Classification of Diseases, Ninth Revision* (ICD-9) coding for stroke (431-434, 436), 10,638 patients were admitted during the study period. Among those patients, 11 were identified to have hyperthyroid via principal ICD-9 diagnoses (242).

Eight patients who met clinical and serologic diagnostic criteria for GD with no other cause of stroke or autoimmune disease were included. Patients with other causes of moyamoya syndrome were excluded. Moyamoya vasculopathy involving the intracranial arteries around the circle of Willis was diagnosed by conventional angiogram (6/8) and magnetic resonance angiography (MRA) in 8/8 patients. Extent of stoke was measured with magnetic resonance diffusion tensor imaging alongside MRA. Data collected included patient demographics (age, sex, ethnicity), vascular risk factors (lipid profile, hypertension, glycosylated hemoglobin), previous history of cerebrovascular diseases, laboratory tests (thyroid studies, rheumatologic studies), treatment, and imaging.

Literature Review

Using the MeSH database system of PubMed, a literature search was performed by searching for all articles containing ("Moyamoya"[Mesh]) AND "Graves disease"[Mesh]. Articles were limited to English, and humans were defined as the subjects. In addition, review articles were excluded. A general PubMed search was also performed, using combinations of the search terms "moyamoya," "Graves," and "thyrotoxicosis." One author reviewed the articles and determined which studies to include or exclude, and discrepancies or indecisions were resolved among the other authors. No studies were found to be duplicates. The last search was performed on 5 October 2015.

Articles were reviewed for patient demographics, onset and duration of GD, onset of moyamoya disease, Suzuki classification, thyroid status at presentation and at surgery, as well as treatment modalities and outcomes. Our review of patient outcomes was based on patients reported in the literature, as well as those from the current series. Based on treatment modality, patients were categorized into 2 treatment groups: medical management and medical management plus neurosurgical prophylaxis. Patients with medical noncompliance were excluded from statistical analysis. Neurosurgical prophylaxis was defined as surgery to prevent future ischemic attacks in otherwise neurologically intact and euthyroid patients. *t* Tests were performed for comparison of age, gender, Suzuki classification, and clinical improvement between the 2 treatment groups.

RESULTS

Demographics and Clinical Presentation

Between 2004 and 2014, we identified 8 patients treated at our institution with both GD and thyrotoxicosis. All 8 patients were female, with an average age of 32 years (range, 19–48 years). Seven patients were of Hispanic/Latin American ethnicity. One patient was white, non-Hispanic. Two patients were a mother–daughter pair and 1 patient had an extensive family history of GD. Per patient history, the duration of thyrotoxicosis symptoms preceding stroke ranged from 2 weeks to 2 years; however, total duration of GD diagnosis was between 0 and 12 years.

In all 8 patients, GD thyrotoxicosis was diagnosed clinically with supportive serology during the setting of acute thyrotoxicosis according to the American College of Endocrinology and the American Association of Clinical Endocrinologists Guidelines.[12,13] Clinically, all patients had goiter and all but 1 patient had ophthalmopathy (patient 5).

All patients presented with acute cerebrovascular ischemia, confirmed with diffusion-weighted magnetic resonance imaging. No patients presented with hemorrhagic stroke (**Table 1**).

Laboratory Data

All patients presented with undetectable thyroid-stimulating hormone (TSH) and increased T4 levels (9.9 ng/dL ± 7.3) at time of acute infarct. Antibodies, including thyroid peroxidase, TSH receptor, and thyroglobulin, were positive in 5/8 patients. Antinuclear antibody levels were normal in all patients. Erythrocyte sedimentation rate was normal in 7/8 patients. None of the patients had clinical features suggestive of primary or secondary central nervous system vasculitis. Cerebrospinal fluid studies were obtained in 4/8 patients and resulted within normal limits.

Radiologic Presentation

Moyamoya vasculopathy was diagnosed by MRA (8/8). Further evaluation with conventional angiography was used for 6/8 patients (**Figure 1**). Bilateral ICA stenosis, with or without stenosis of the proximal MCA and ACA, was seen in all patients. Magnetic resonance diffusion tensor imaging alongside MRA was used to characterize the extent of stroke (**Figure 2**).