Neurovascular Complications of Marfan Syndrome
A Retrospective, Hospital-Based Study

Robert J. Wityk, MD; Carla Zanferrari, MD; Stephen Oppenheimer, MD, PhD

Background and Purpose—Small case series have associated Marfan syndrome with cerebral and spinal ischemia or hemorrhage. However, there has been no investigation of the frequency and etiology of neurovascular disorders in a large series of Marfan patients.

Methods—We conducted a retrospective, hospital-based study of all Marfan syndrome patients seen in an 8-year period. Records were reviewed in detail, and clinical characteristics of those with and without a neurovascular diagnosis compared.

Results—Of 513 patients, 18 (3.5%) had a neurovascular diagnosis, as follows: transient ischemic attack (11), cerebral infarction (2), spinal cord infarction (2), subdural hematoma (2), and spinal subarachnoid hemorrhage (1). A cardioembolic source was identified in 12 of 13 patients with cerebral ischemia, as follows: prosthetic heart valves (9), mitral valve prolapse (2), and atrial fibrillation (1). Chronic anticoagulant therapy was a likely cause in 2 of 3 patients with hemorrhagic events. Compared with other Marfan syndrome patients, those with neurovascular events were older (39.6 versus 31.7 years, \( P = 0.04 \)) and more likely to be in atrial fibrillation (22.2% versus 3.2%, \( P < 0.01 \)), to have prosthetic heart valves (61.1% versus 7.7%, \( P = 0.001 \)), and to be taking anticoagulant therapy (72.2% versus 16.1%, \( P < 0.001 \)). Aortic disease, a putative factor in the etiology of neurovascular complications, was present in equal measure in Marfan patients with and without neurovascular complications (78% versus 65%, \( P = NS \)).

Conclusions—Neurovascular complications of Marfan syndrome are rare during 8 years of follow-up, and generally are ischemic in nature. A high-risk cardiac source was identified in the majority. A significant association with vascular dissection was not established. (Stroke. 2002;33:680-684.)

Key Words: cerebral ischemia, transient • Marfan syndrome • stroke

Marfan syndrome is an autosomal-dominant disorder of connective tissue with musculoskeletal, ocular, and cardiovascular manifestations.1–3 Mutations in the gene encoding fibrillin on chromosome 15 constitute the likely underlying cause in the majority of cases. Clinical expression of the genetic defect, however, can be variable both within and between families.4–6 In large and medium-sized arteries, defects in fibrillin are associated with disruption of elastic fibers, predisposing to aneurysm formation and arterial dissection.7 These vascular abnormalities can be a cause of cerebral and spinal ischemia or hemorrhage.3,8–16 Indeed, ischemic events involving the brain or spinal cord are estimated to occur in 10% to 20% of patients with Marfan syndrome.3

Aortic dissection is a major contributor to the premature mortality of Marfan syndrome. Extension of a dissecting aortic aneurysm into the brachiocephalic and common carotid arteries may lead to ischemic stroke.17,18 However, patients with Marfan syndrome have been reported to have dissection of cerebral arteries independent of aortic disease, and several textbooks include Marfan syndrome in the differential diagnosis of spontaneous cerebral artery dissection.8,9,19–21

Knowledge of the vascular complications of Marfan syndrome has come mainly from case reports involving small numbers of patients with the concomitant potential for selection bias. Two recent studies, however, cast doubt on the supposed association between cerebral aneurysm and Marfan syndrome.22,23 No investigation of the prevalence and nature of neurovascular complications has been performed in a large group of patients. We therefore undertook a retrospective, hospital-based study of Marfan patients followed in the specialized Marfan clinic or admitted to the Johns Hopkins Hospital (JHH) over an 8-year period to assess the frequency, presentation, and etiology of neurovascular complications this disorder.

Subjects and Methods

Both inpatients and outpatients seen at JHH between 1989 and 1997 were included in the study. The diagnosis of Marfan syndrome was made using the criteria of McKusick and Pyeritz and the later “Berlin nosology.”1–2 Two different methods for case ascertainment were

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applied. For admissions, use was made of a computerized database of hospital discharge diagnoses for inpatients admitted during the study period using the International Classification of Diseases (9th revision) code for Marfan syndrome (759.82) and a broad range of codes for neurovascular disease (430.xx to 438.xx). The medical records and imaging studies of all possible matches were reviewed to confirm the diagnosis of Marfan syndrome and cerebrovascular disease. For outpatients, all charts of patients seen in the Marfan clinic during the study period were reviewed for the occurrence of any neurovascular disorder. This clinic is a tertiary multidisciplinary unit staffed by geneticists and a neurological consultant with expertise in genetic disorders drawing patients from a large geographic location. Families are assigned a pedigree code after confirmation of the diagnosis, so that records from several affected family members may be reviewed in one file.

Patients with possible neurovascular symptoms or findings were identified, and all available studies, including imaging, were reviewed. Each case was scrutinized by two neurologists with a specialized interest in vascular disorders of the nervous system (R.J.W. and S.O.) to confirm a diagnosis of stroke or transient ischemic attack (TIA) and attribute etiology. We followed the guidelines of the Classification of Cerebrovascular Diseases III24 for defining TIA and ischemic/hemorrhagic stroke, and used the TOAST Classification (Trial of Org 10172 in Acute Stroke Treatment)25 for sources of cardioembolism. Clinical and demographic characteristics as well as the presence of stroke risk factors were identified and compared in Marfan patients with and without neurovascular complications.

Comparisons were made using a Fisher exact test for categorical variables or a two-sided Student t test for continuous variables. Vascular risk factors for Marfan patients without cerebrovascular disease were collected from outpatient charts only.

Results

We reviewed 513 patients with Marfan syndrome seen during the study period, of whom 244 were inpatients and 269 outpatients. There were 300 males and 213 females, with an overall mean age of 31.7 years (range 0.1 to 81 years). The mean duration of follow-up was 8.3 years (range 1 to 38 years). We found 20 Marfan syndrome patients with a concomitant neurovascular diagnosis. Two patients were excluded; 1 patient had insufficient documentation to support the diagnosis, and in another, the reported carotid artery abnormality was not confirmed on further testing. Thus, the overall number of Marfan syndrome patients with a neurovascular disorder was 18 (3.5%), comprising 9 males and 9 females, with a mean age of 39.6 years (range 0.25 to 72 years) (Table 1).

Ischemic events occurred in 15 of 18 patients (83%). Eleven patients had TIAs, which were recurrent in 3. The most common TIA symptoms were visual disturbances in 5 patients (with suspected retinal ischemia in 3) and paresthesias in 4 patients. Two patients had vertebrobasilar TIAs, and only 1 had hemiparesis. Two patients had hemispheric infarcts. One developed mild hemiparesis after cardiac valve surgery, and the other had a middle cerebral artery territory infarct after pacemaker placement in the setting of atrial fibrillation. Two patients had spinal cord infarcts, both with dissecting thoracic aortic aneurysms. In 1 patient, the spinal cord infarction was thought to be directly related to aortic dissection, but the other patient had a complicating factor of infection and possible septic embolism.

The mechanism of stroke or TIA was uncertain in some patients because of limited diagnostic testing. In most of these patients, the etiology was presumed by the primary physicians to be cardioembolic in nature, and detailed vascular evaluation was not performed. Among 13 patients with cerebral ischemia, 6 had brain imaging studies and 3 had carotid duplex ultrasound performed for evaluation of the neurological event. However, a high-risk cardiac source of embolism was present in 10 of 13 patients (77%), including prosthetic cardiac valves in 9 patients (3 of whom also had atrial fibrillation) and atrial fibrillation in 1 patient. All 10 patients were being treated with anticoagulants. Of the remaining 3 patients with cerebral ischemia, 2 had mitral valve prolapse as a potential source of embolism, and 2 were being treated with antiplatelet agents. Of note was the high proportion of patients with cerebral ischemia who had a history of ascending aortic aneurysms documented by echocardiography (11 of 13 patients, 85%).

Hemorrhagic events occurred in 3 patients (17%). Two patients had subdural hematomas. One was a child with aortic and mitral valve prolapse who presented with autonomic dysfunction and seizures. The mechanism of the subdural bleeding was uncertain. Another patient presented with bilateral subdural hematomas while on chronic anticoagulation for a prosthetic heart valve. Finally, 1 patient presented with spinal subarachnoid hemorrhage and paraplegia while on chronic anticoagulation for a prosthetic heart valve. The patient died suddenly a week later from cerebral subarachnoid hemorrhage. Autopsy revealed vertebrobasilar dolichoectasia with suspected rupture of a vertebral artery.16

Clinical characteristics of patients with Marfan syndrome and neurovascular disorders were compared with other Marfan syndrome patients (Table 2). Patients with neurovascular disorders tended to be older than other Marfan syndrome patients (mean age 39.6 versus 31.7 years, P=0.04) and were more likely to have atrial fibrillation (22.2 versus 3.2%, P<0.01) and prosthetic heart valves (61.1 versus 7.7%, P=0.001) and to be on anticoagulant therapy (72.2 versus 16.1%, P<0.001). There was no significant association with other common risk factors for stroke, such as hypertension, diabetes, or smoking, although these factors were uncommon in this patient population. Proximal aortic enlargement was equally common in both groups (77.7% versus 64.8%, P=N.S.).

We found no patient in our review with either a cerebral aneurysm or suspected aneurysmal subarachnoid hemorrhage. There were also no patients found with isolated cerebral artery dissection, although, as mentioned above, extensive vascular imaging was not performed in most patients.

Discussion

Case reports in the literature suggest an association of Marfan syndrome with cerebral aneurysm and cerebral arterial dissection. Pathological examination in some of these reports suggests an etiologic relationship of Marfan syndrome with the disorder, but in the absence of a population-based study, the true risk of stroke or TIA in Marfan syndrome patients is uncertain. In the present study, we present a retrospective, hospital-based survey of neurovascular disorders associated with Marfan syndrome, drawing from records of patients seen...
over an 8-year period at a tertiary referral center with a longstanding interest in Marfan syndrome. We attempted to capture all Marfan syndrome patients seen at our institution during the study period by extensive review of inpatient and outpatient records, in the hopes of describing the most common neurovascular events associated with this syndrome.

The overall frequency of neurovascular disorders was 3.5% in our study. Ischemic events outnumbered hemorrhagic

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Risk Factors</th>
<th>Type of Event</th>
<th>Description</th>
<th>Diagnostic Tests</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>Asc. aortic aneurysm, prosthetic valve, aortic graft</td>
<td>TIA (2 episodes)</td>
<td>Left-sided numbness soon after surgical replacement of cardiac valves</td>
<td>None</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>M</td>
<td>Asc. aortic aneurysm, mitral valve prolapse</td>
<td>TIA</td>
<td>Transient left-sided dysesthesia</td>
<td>Carotid duplex, TEE</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>F</td>
<td>Asc. aortic aneurysm, mitral valve prolapse</td>
<td>TIA</td>
<td>Right amaurosis fugax</td>
<td>Carotid duplex, TEE</td>
<td>Antiplatelet agent, beta-blocker</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>F</td>
<td>Asc. aortic aneurysm, prosthetic valve</td>
<td>TIA</td>
<td>Blurred vision, suspected retinal emboli</td>
<td>CT scan</td>
<td>Anticoagulant, beta-blocker</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>M</td>
<td>HTN, hyperlipidemia, asc. aortic aneurysm, prosthetic valve</td>
<td>TIA</td>
<td>Transient disequilibrium, visual distortion</td>
<td>None</td>
<td>Anticoagulant, beta-blocker</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>M</td>
<td>Prosthetic valve, atrial fibrillation</td>
<td>TIA (2 episodes)</td>
<td>Soon after surgical replacement of cardiac valves</td>
<td>TTE, TEE</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>M</td>
<td>Asc. aortic aneurysm, prosthetic valve, atrial fibrillation</td>
<td>TIA</td>
<td>Transient left facial numbness, blurred vision</td>
<td>MRI</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>M</td>
<td>Asc. aortic aneurysm, mitral valve prolapse, prosthetic valve</td>
<td>TIA</td>
<td>Transient vertebrobasilar symptoms</td>
<td>None</td>
<td>Anticoagulant, aspirin, beta-blocker</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>F</td>
<td>Prosthetic valve, atrial fibrillation</td>
<td>TIA (2 episodes)</td>
<td>Transient right-sided weakness; left facial numbness</td>
<td>CT</td>
<td>Anticoagulant, beta-blocker</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>F</td>
<td>Asc. aortic aneurysm</td>
<td>TIA</td>
<td>No details</td>
<td>None</td>
<td>Antiplatelet agent, beta-blocker</td>
</tr>
<tr>
<td>11</td>
<td>72</td>
<td>F</td>
<td>Asc. aortic aneurysm, prosthetic valve</td>
<td>TIA</td>
<td>Blurred vision, suspected retinal emboli</td>
<td>Carotid duplex, MRI</td>
<td>Anticoagulant, beta-blocker</td>
</tr>
<tr>
<td>12</td>
<td>31</td>
<td>M</td>
<td>Asc. and desc. aortic aneurysm, prosthetic valve, aortic graft, CABG</td>
<td>Hemispheric infarction</td>
<td>Left-sided mild weakness soon after surgical replacement of cardiac valves, generalized seizure</td>
<td>CT</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>F</td>
<td>Hyperlipidemia, atrial fibrillation, heart block, aortic dissection</td>
<td>Hemispheric infarction</td>
<td>Left-sided hemiplegia, hemianopsia, and hemihemianesthesia soon after pacemaker placement</td>
<td>CT, TTE, Holter ECG</td>
<td>Anticoagulant</td>
</tr>
<tr>
<td>14</td>
<td>0.25</td>
<td>F</td>
<td>Aortic and mitral valve prolapse</td>
<td>Subdural hematoma</td>
<td>Seizure</td>
<td>CT, MRI, EEG, TEE</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>27</td>
<td>M</td>
<td>Asc. aortic aneurysm, prosthetic valve</td>
<td>Subdural hematoma (bilateral)</td>
<td>None</td>
<td>CT, MRI, MRA</td>
<td>Anticoagulant (at time of onset of symptoms)</td>
</tr>
<tr>
<td>16</td>
<td>39</td>
<td>M</td>
<td>Asc. and desc. aortic aneurysm, mitral valve prolapse, prosthetic valve</td>
<td>Spinal cord infarction</td>
<td>Paraplegia (complication of desc. aorta aneurysm dissection)</td>
<td>MRI thorax-abdomen</td>
<td>Anticoagulant, beta-blocker</td>
</tr>
<tr>
<td>17</td>
<td>60</td>
<td>F</td>
<td>HTN, asc. and desc. aortic aneurysm</td>
<td>Spinal cord infarction</td>
<td>Right leg paresis, septic embolism, death</td>
<td>Spinal angiogram, MRI thorax-abdomen</td>
<td>Beta-blocker, antibiotics</td>
</tr>
<tr>
<td>18</td>
<td>37</td>
<td>F</td>
<td>HTN, asc. aortic aneurysm, aortic graft</td>
<td>Spinal SAH, later cerebral SAH</td>
<td>Paraplegia with neck pain: 1 week later, sudden coma and death</td>
<td>CT, spinal MRI, spinal angiogram</td>
<td>Anticoagulant (at time of onset of symptoms)</td>
</tr>
</tbody>
</table>

Asc. indicates ascending; desc., descending; HTN, hypertension; TIA, transient ischemic attack; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; CABG, coronary artery bypass graft; and SAH, subarachnoid hemorrhage.
TABLE 2. Clinical Characteristics of Marfan Syndrome Patients With Neurovascular Disorders

<table>
<thead>
<tr>
<th>Marfan Patients</th>
<th>Marfan Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With NVD (n=18)</td>
<td>Without NVD (n=495)</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean)</td>
<td>39.6</td>
<td>31.7</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>50</td>
<td>58.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>16.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Lipid disorder (%)</td>
<td>11.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Prosthetic heart valve (%)</td>
<td>61.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Mitral valve prolapse (%)</td>
<td>27.7</td>
<td>48.8</td>
</tr>
<tr>
<td>Aortic valve prolapse (%)</td>
<td>5.5</td>
<td>15.0</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>22.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Aortic enlargement (dilatation or aneurysm) (%)</td>
<td>77.7</td>
<td>64.8</td>
</tr>
<tr>
<td>Aortic dissection (%)</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Aortic root graft (%)</td>
<td>16.6</td>
<td>9.7</td>
</tr>
<tr>
<td>Anticoagulant use (%)</td>
<td>72.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Antiplatelet agent use (%)</td>
<td>11.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Beta-blocker use (%)</td>
<td>55.5</td>
<td>67.0</td>
</tr>
</tbody>
</table>

NVD indicates neurovascular disorder.

events 5 to 1 in this group of patients. The Marfan syndrome patients we reviewed were in general a young population (average age <40 years) with few of the usual vascular risk factors associated with atherosclerotic stroke. However, cardiac abnormalities such as prosthetic heart valves, atrial fibrillation, mitral valve prolapse, and aortic root dilation were common, as expected from the known clinical features of the disorder. We found that neurovascular disorders in patients with Marfan syndrome were more likely related to a cardiac source of embolism, particularly prosthetic heart valves and atrial fibrillation. Neurovascular patients were also more likely to be on treatment with anticoagulant or antiplatelet agents, and in two cases, anticoagulant use likely contributed to a hemorrhagic neurological event. Neurovascular patients were similar to other Marfan patients, however, in terms of traditional stroke risk factors, such as hypertension, diabetes, smoking, or lipid disorders, suggesting that atherosclerosis was not a major factor in etiology. The cardiac disorders associated with Marfan syndrome and their treatment appear to be the most common causes for neurovascular complications in this patient group.

We found no patient in our review with cerebral artery dissection. Cystic medial necrosis and disruption of elastic fibers are common findings in Marfan syndrome and may predispose to spontaneous cerebral arterial dissection independent of aortic dissection.19,26 Austin and Schaefer19 reported a 25-year-old man with Marfan syndrome who presented with a right hemispheric stroke and loss of the right brachial and carotid pulses. Autopsy revealed mitral valve prolapse, aortic root dissection, and independent dissections of the distal innominate artery (with right internal carotid artery occlusion) and the distal left common carotid artery.

Finney et al10 reported a retrograde dissection in a patient who underwent clamping of the internal carotid artery during treatment of a giant cavernous carotid aneurysm. Youl et al15 described a patient with Marfan syndrome with spontaneous internal carotid artery dissection followed later by an asymptomatic vertebral artery dissection. Schievink et al19 reported a patient with Marfan syndrome who had bilateral carotid artery dissections; the right carotid artery lesion was related to an ascending aortic dissection, whereas the left carotid artery dissection was independent of the aortic lesion, but associated with pathological changes of fibromuscular dysplasia. Several other authors have reported patients with suspected Marfan syndrome or a family history of Marfan syndrome who were found to have pathological evidence of cystic medial necrosis associated with cerebral artery dissection.27–29 Review of our stroke database showed that approximately 20 to 30 patients are seen each year at our institution with a diagnosis of cerebral artery dissection, but none with Marfan syndrome. However, detailed diagnostic evaluation of the cerebral vasculature was under-utilized in the Marfan syndrome patients we reviewed, particularly in patients with a potential cardiac source of embolism, so cerebral arterial dissection in these patients may have been missed. The true incidence of cerebral artery dissection in Marfan syndrome will require further study with systematic assessment of the cerebral vasculature.

Extension of proximal aortic dissection into the brachiocephalic or spinal arteries is another potential mechanism for stroke.17,18 Acute aortic dissection was implicated as an etiology in only one of our cases—a patient with spinal cord infarction—but in no case was extension of aortic dissection into a cervical artery found as a cause of hemispheric stroke. Magnetic resonance angiography (MRA) offers a noninvasive means of identifying carotid and sometimes vertebral artery dissection, and gadolinium-enhanced MRA of the aortic arch and proximal brachiocephalic arteries may be the optimal screening test to investigate patients with Marfan syndrome who have cerebral ischemia.30,31

An association of cerebral aneurysm with Marfan syndrome has recently been called into question. van den Berg et al22 reviewed the records of 135 patients followed in a Marfan clinic in Amsterdam and failed to discover a single case of cerebral aneurysm or subarachnoid hemorrhage.22 Follow-up was a mean of 4.5 years in 129 of these patients. One patient developed a lobar intracerebral hemorrhage in the setting of alcohol and barbiturate intoxication. A cerebral angiogram was negative for aneurysm or vascular malformation. Conway et al.23 at our institution, reviewed all patients with Marfan syndrome who came to autopsy at JHH between 1939 and 1996. Among 25 autopsies, 1 patient was found to have a small, asymptomatic, anterior-communicating artery aneurysm, resulting in a prevalence of intracranial aneurysm not statistically different from the general population. A further review of 710 neurosurgical patients treated at JHH for intracranial aneurysm from 1990 to 1998 revealed no patient with Marfan syndrome.23

In the past, life expectancy in patients with Marfan syndrome appeared to be shortened by more than one third as a result of cardiovascular complications, particularly aortic regurgitation and dissecting aortic aneurysm.32,33 Three of our
patients had ischemic events occurring shortly after surgery for prosthetic valve replacement and/or placement of an aortic root graft. Gott et al. reported postoperative cerebral embolic events in 25 of 675 patients (3.7%) undergoing aortic root replacement. The close follow-up of aortic root diameter by serial ultrasound measurements, the use of prophylactic beta-blockers, and the availability of safer cardiovascular surgery in patients with Marfan syndrome may alter the natural history of associated neurovascular diseases in this patient population. Marfan patients may be surviving longer and are now exposed to other potential causes for neurovascular disorders.

In conclusion, patients with Marfan syndrome in our series had a diverse spectrum of neurovascular disorders, but the etiology of both ischemic and hemorrhagic events did not appear to be directly related to the primary connective tissue defect in Marfan syndrome. Instead, as Marfan syndrome patients live longer, they may see greater exposure to the chronic risks of embolism from cardiac sources or complications of anticoagulant therapy.

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References
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