May-Thurner Syndrome in Patients With Cryptogenic Stroke and Patent Foramen Ovale

An Important Clinical Association

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Background and Purpose—We aimed to investigate the incidence of May-Thurner syndrome in patients with cryptogenic stroke with patent foramen ovale.

Methods—This was a retrospective study. All consecutive patients with cryptogenic stroke having undergone patent foramen ovale closure from January 1, 2002, to December 31, 2007, at our institute were included in this study. Pelvic magnetic resonance venography studies of all patients were reviewed to determine if features of May-Thurner syndrome were present. Medical records and invasive venography studies of all patients were reviewed when available. All patients with May-Thurner syndrome features on magnetic resonance venography were reviewed by a vascular medicine specialist to define any previous incidence of deep vein thrombosis or any signs of chronic venous insufficiency. All patients also had lower limb venous duplex performed to rule out lower limb venous thrombosis.

Results—A total of 470 patients from January 1, 2002, until December 31, 2007, with cryptogenic stroke underwent patent foramen closure at our institute. Thirty patients (6.3%) had features consistent with May-Thurner syndrome on magnetic resonance venography. These patients were predominantly female (80%) with a mean age of 43.6±11.9 years. Twelve patients (40%) had abnormalities in their laboratory thrombophilia evaluation and 13 females (54.1%) were taking hormone-related birth control pills. Only 2 patients had a history and signs of chronic venous insufficiency. All patent foramen ovales demonstrated right-to-left shunting on transesophageal echocardiography. Atrial septal aneurysms/hypermobile atrial septa were present in 70% of patients with May-Thurner syndrome.

Conclusion—May-Thurner syndrome has an important clinical association with cryptogenic stroke and patent foramen ovale. (Stroke. 2009;40:1502-1504.)

Key Words: PFO ■ May Thurner syndrome ■ cryptogenic stroke ■ iliac vein thrombosis
MRV. All patients also had lower limb venous duplex performed to rule out lower limb venous thrombosis.

To be considered for transcatheter PFO closure at our center, patients must have had ≥1 preceding focal neurological event(s) consistent with stroke/transient ischemic attack considered by the PFO Committee (neurologist/invasive and noninvasive cardiologist/hematologist) to have been most likely caused by a paradoxical embolus. Moreover, the PFO Committee considered the presence of a significant right-to-left shunt at rest, an atrial septal aneurysm/hypermobile atrial septum, persistent eustachian valve, or Chiari network as high-risk characteristics.

Statistical Analysis
All data were entered into a computerized database. Statistical analysis was performed using Statistical Analysis Systems, Version 8.2 (SAS Institute, Cary, NC). Data are expressed as means±SDs for continuous variables and as percentages for categorical data. Student t test was used to compare continuous variables and the χ² test or Fisher exact test for categorical values. Univariate analysis was conducted to identify the predictors of adverse outcomes, and, if significant, these were tested in a multivariate regression analysis model. A probability value <0.05 was considered statistically significant.

Results
Between January 1, 2002, and December 31, 2007, a total of 470 patients with cryptogenic stroke underwent PFO closure at our institution. Thirty patients (6.3%) had features consistent with MTS on MRV. The remaining 440 patients without features of MTS on MRV but having undergone PFO closure in association with cryptogenic stroke were also analyzed as shown in the Table. Patients with MTS were younger and predominantly female. The prevalence of cardiovascular risk factors, including hypertension, hypercholesterolemia, and diabetes, was higher in the group without features of MTS, albeit not significantly. Interestingly, there was a statistically significant higher prevalence of active smokers in the MTS group. All PFOs demonstrated right-to-left shunting on transesophageal echocardiography. There was no difference in the incidence of atrial septal aneurysms/hypermobile atrial septum. The mean closure device size did not differ between the groups.

Table. Cryptogenic Stroke and PFO: Clinical Features of Patients With MTS and Without MTS

<table>
<thead>
<tr>
<th></th>
<th>MTS-Negative</th>
<th>MTS-Positive</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (%)</td>
<td>440 (93%)</td>
<td>30 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>49.2±14.3</td>
<td>43.6±11.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Female sex</td>
<td>232 (53%)</td>
<td>24 (80%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>136 (31%)</td>
<td>4 (14%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>165 (38%)</td>
<td>4 (14%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current smoker</td>
<td>33 (8%)</td>
<td>8 (27%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>64 (15%)</td>
<td>4 (14%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (5%)</td>
<td>5 (2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypercoagulable condition</td>
<td>103 (24%)</td>
<td>12 (40%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Atrial septal aneurysm/hypermobile atrial septa</td>
<td>301 (68%)</td>
<td>21 (70%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Device size</td>
<td>21.25±7.12</td>
<td>21.25±/-.7.10</td>
<td>1.0</td>
</tr>
</tbody>
</table>
stents; both patients had thrombotic occlusions of the left common iliac veins, presence of collateral vessels, and hemodynamically significant gradients on pressure measurements.

Discussion

The pathogenesis of MTS is not completely understood, but it is theorized that it may be a combination of both mechanical compression and arterial pulsations by the right iliac artery leading to the development of intimal hypertrophy within the wall of the left common iliac vein. This can lead to potential endothelial changes, thrombus formation, and possible cryptogenic stroke in the context of a PFO. The overall incidence of the condition is unknown with one study reporting 37% of 24 patients with isolated left lower extremity edema having left iliac vein compression by MRV.5 Patients with MTS tend to be young women, in the second to fourth decade of life, after periods of prolonged immobilization or pregnancy. In 1992, Kim et al described 3 clinical stages of the disease associated with iliac vein compression: Stage I, asymptomatic; Stage II, development of a venous “spur”; and Stage III, thrombosis of the left common iliac vein. The relevance of Stage I to cryptogenic stroke in the context of PFO is unknown.

Although the association between MTS and cryptogenic stroke was previously reported in case reports,3,4 the current study is the first large-scale analysis of the association between MTS, cryptogenic stroke, and PFO. In our study, we found an incidence of MTS of 6.3% in patients diagnosed with cryptogenic stroke having undergone PFO closure. The majority of these patients were asymptomatic from lower limb venous obstructive symptoms with MTS representing an incidental diagnosis. However, in the context of a previous embolic event, it is conceivable that asymptomatic MTS may be an important clinical association and these patients should be screened by MRV. When compared with the gold standard of contrast venography, MRV has been reported to have 100% sensitivity and 98% specificity in the detection of deep vein thrombosis.7 Many studies have indicated that there is a higher incidence of pelvic/lower extremity thrombi in patients with PFO-associated cryptogenic stroke.8–12

Paradoxical emboli as a cause of cryptogenic stroke in association with PFO are most probably small emboli that traverse through the cardiac chambers en route to the cerebral circulation.13-15 The small size of these emboli probably reflect their propensity to cause stroke instead of clinically significant pulmonary emboli. Modern-day vena cava filters do not have the capacity to prevent small emboli reaching the right heart from the pelvic/lower limb venous circulation.

The direction of flow from the inferior vena cava toward the interatrial septum is also important in the genetics of paradoxical emboli in PFO-related cryptogenic stroke. A persistent eustachian valve is a frequent finding in patients with a PFO.16 By directing the blood from the inferior cava to the interatrial septum, a persisting eustachian valve may indirectly predispose to paradoxical systemic embolization in patients with MTS instead of causing pulmonary emboli.

Limitations

This study is limited by being a retrospective study in a high-risk population at a specialized tertiary care center. However, we feel that the results are generalizable to a high-risk stroke population at other centers. In addition, women tend to have a more complex pelvic structure and MRV sometimes may not give the best visualization of the venous vasculature.

Conclusion

May-Thurner syndrome has an association with cryptogenic stroke in the context of a PFO. In young patients (<55 years) with cryptogenic stroke and PFO, especially with associated use of oral contraceptives, thrombophilic abnormalities, or presence of an atrial septal aneurysm, MTS represents an important condition and warrants screening by MRV. Further prospective studies are needed to define in greater detail the association of MTS with PFO-associated cryptogenic stroke.

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Disclosures

None.

References

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