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 ovale 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

Iliocaval compression, or May-Thurner syndrome (MTS), was initially described as the development of “spurs” in the left iliac vein as a consequence of compression from the contralateral right common iliac artery against the lumbar vertebra is an anatomic variant that is well recognized (Figure 1). Apart from case reports, the association of MTS with cryptogenic stroke in the context of a patent foramen ovale (PFO) has not been studied. The incidence of MTS in patients with cryptogenic stroke and PFO is unknown. We endeavored to perform a formal analysis of this understudied cohort of patients.

Methods
All consecutive patients with cryptogenic stroke as documented clinically by the referring neurologist and by CT/MRI having undergone PFO closure from January 1, 2002, to December 31, 2007, at our institution were included in this study. Cryptogenic stroke was defined as a sudden focal neurological event in the absence of an identifiable cause such as uncontrolled hypertension, intracranial hemorrhage, ipsilateral carotid lesion, atrial fibrillation, intracardiac thrombus, degenerative neurological disorder, or neoplasm. All patients underwent a comprehensive workup to rule out all of the previously mentioned conditions. This workup included CT angiography and/or MR angiography, extracranial duplex ultrasonography of the carotid arteries, 24-hour Holter monitoring, transthoracic±transesophageal echocardiography, and a hypercoagulability evaluation.

Pelvic magnetic resonance venography (MRV) studies of all patients were reviewed to determine if features of MTS were present. On the basis of MRV findings, MTS was defined as the presence of deep venous thrombosis in the left common iliac vein or stenosis of the left common iliac vein (Figure 2). Available medical records and invasive contrast venography studies of all patients were reviewed. To define any previous incidence of deep vein thrombosis or signs of chronic venous insufficiency, a vascular medicine consultation was obtained in all patients with the previously defined MTS features on
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 septa. The mean closure device size did not differ between the groups.

There was a statistically significant higher incidence of laboratory thrombophilia screen abnormalities in the MTS group (Table). Twelve patients within the MTS group had abnormalities of their laboratory thrombophilia screen; these included the prothrombin gene mutation (G20210A; 2 patients), Factor V Leiden mutation (2 patients), elevated anticardiolipin antibody titer (4 patients), documented antiphospholipid syndrome (one patient), and protein C (one patient) or protein S deficiency (2 patients). Of the female patients in the MTS group, 13 females (54.1%) were taking oral contraceptives, 2 females (8.3%) were using hormone-eluting intrauterine contraceptive devices, and one patient was 8 weeks pregnant at the time of cerebral embolic event.

Only 2 patients had a history and/or signs of chronic venous insufficiency. One patient had a history of multiple previous left-sided deep vein thromboses. Five patients in total underwent contrast iliac venography for the indications of signs and symptoms of chronic venous insufficiency and query iliac vein thrombus on MRV. Only 2 patients (6.6%) with MTS underwent percutaneous stenting of the left iliac vein with self-expanding...
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 al3 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 6.5% 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 genesis 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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