Lettere all’Editore

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Atrial septal defect and hyperhomocysteinemia: two culprits for a cryptogenic stroke

To the Editor. Recent data have implicated an otherwise unrecognized atrial septal defect to explain at least a proportion of cryptogenic strokes and the so-called non-traditional risk factors, which include hyperhomocysteinemia and other prothrombotic conditions, are also likely to play a role in this setting.

A 63-year-old, right-handed man presented with recurrent neurological symptoms. The patient had been well until 8 days earlier, when he briefly had numbness of the right side of the mouth and tongue and vertical diplopia that resolved after 30 min. The vertical diplopia briefly recurred the next morning when the patient later also had an episode of vertigo. On the day of admission the diplopia again recurred and persisted for several hours.

The patient had an unremarkable previous medical history, had stopped smoking 6 years previously, and denied alcohol consumption. There was no family history of stroke or aneurysm. On admission, his vital parameters were normal and physical examination of the heart, chest, and abdomen was normal except for a fixed splitting of the second heart sound and a systolic bruit along the left sternal border; no bruits were audible around the neck. On neurological examination, the patient was alert and fully oriented with an intact memory and naming ability; no focal weakness, hemisensory alterations, difficulty with language or slurred speech was noted. The motor function was graded at 5/5 throughout, with normal tone. His sensory functions (light touch, pinprick, vibration, and joint position) were intact. The results of a finger-to-nose and a heel-knee-shin test were also normal; his gait and stance were normal and Romberg’s sign was absent. The deep-tendon reflexes were ++ bilaterally and the left plantar response was flexor; a doubtful right Babinski reflex was noted. The patient reported “blurry vision” when his right eye was uncovered and diplopia when gazing upwards but there was no nystagmus. Examination of the remaining cranial nerve functions was normal.

A computed tomography scan of the head performed with the injection of contrast material revealed an acute, large ischemic lesion in the territory of the left posterior cerebral artery with several small hypointense lesions disseminated throughout the white matter that were judged to be old cerebral infarcts. These findings were confirmed at gadolinium-enhanced magnetic resonance imaging.

The results of the laboratory tests were within the normal limits, except for the plasma homocysteine levels which were increased (28 μmol/L; normal range, 0-12 μmol/L). No lupus anticoagulant and anticardiolipin and antiphospholipid antibodies were detected and the polymerase chain reaction for the prothrombin-gene mutation G2021A and factor V Leiden was also negative. The blood levels of protein C and S were normal and rheumatoid factor and antinuclear and antineutrophil cytoplasmic antibodies were not detected.

A Doppler ultrasonography of the epiaortic vessels yielded a normal outcome and transthoracic echocardiography showed a mildly enlarged right ventricle with no paradoxical movement of the interventricular septum and a hypermobile atrial septum, which suggested the presence of an atrial septal defect or aneurysm, but no intracardiac shunting was documented. A two-dimensional transesophageal echocardiography was performed using an omniplane transducer following the intravenous injection of saline. A floppy atrial septum with a large defect (14 mm) was detected. The flap was observed to move in
response to the cardiac cycle and respiratory motion. Color Doppler ultrasonography showed a left-to-right shunt and, after saline injection, microbubbles appeared in the left atrium during the Valsalva maneuver. This confirmed the presence of an atrial septal defect associated with spontaneous or inducible right-to-left interatrial shunting.

The patient was treated with aspirin and folate and recovered fully. Five weeks later, the atrial septal defect was successfully closed using a transcatheter device, and the subsequent course was uneventful with no complications. When last seen 18 months after the procedure, still on aspirin and folate, the patient was doing well and did not report any relapse of stroke or transient ischemic attack or any other thromboembolic event. At this time, his blood levels of homocysteine were normal and transthoracic echocardiography showed a well positioned device with no residual intracardiac shunting.

A patent atrial septal defect is detected in an ever increasing proportion of patients with a diagnosis of cryptogenic stroke. Paradoxical embolism, with the passage of emboli from the right to the left atrium across the patent atrial septal defect, is the most likely mechanism of stroke but a thrombus has been occasionally imaged while transiting through the atrial septal defect; other mechanisms of stroke could include in situ thrombosis within the canal of the patent foramen ovale and associated atrial arrhythmias.

The association with stroke may be stronger if a concomitant hypercoagulable state is also present and two recent studies have indeed demonstrated a greater risk of cerebral infarction among patients with an atrial septal defect carrying the prothrombin G20210A variant or factor V G1691A mutation. Our patient was found to have elevated blood levels of homocysteine, which is known to constitute an independent predisposing factor to thrombosis, and this may reliably confer a strong and additional risk for stroke in this setting. Even though the link between hyperhomocysteinemia and venous thrombosis is not as solid as its link with arterial vascular disease, we infer that hyperhomocysteinemia did play a role in the thromboembolic complication occurring in this patient. The mechanism of hyperhomocysteinemia in this case is unclear. One important point is that the patient was not exposed to any folate or vitamin B6 antagonist, such as methotrexate, phenytoin, estrogens, tobacco, or theophylline, which also increase the homocysteine concentrations. Besides, an acquired nutritional folate deficiency does not sound very convincing as a pathogenetic cause.

Our patient had his atrial septal defect successfully repaired by implantation of a transcatheter device, and this is in full agreement with recent evidence emphasizing this procedure as an effective and low-risk strategy for the management of such patients.

We suggest that the possibility of an atrial septal defect be borne in mind even when older patients present with an otherwise unexplained stroke. The association of a patent atrial septal defect with hyperhomocysteinemia may expose such patients to a particularly high risk of stroke or other embolic events.

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References