

When You Can't Identify the Cause of a Stroke: Advanced and Specialized Tests

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Your patient has a stroke, and you do an appropriate initial workup looking for large-artery atherosclerosis, cardioembolism, and small-vessel disease. A specific cause is not discovered. Symptomatic cerebral infarcts for which no cause is found after an adequate, standard diagnostic evaluation (defined below) are called *cryptogenic strokes*.¹

Rather than representing a minority of all central nervous system ischemic events, cryptogenic strokes account for 10% to 40% of all ischemic strokes (with the best estimate being approximately 25%).¹ A timely Top Paper¹ addresses the state of the art for an approach to cryptogenic strokes.

The contemporary evaluation of strokes includes magnetic resonance imaging (MRI), vessel anatomy imaging (computed tomography or magnetic resonance angiography, carotid duplex ultrasonography, or Doppler ultrasonography), echocardiography, occasionally transesophageal echocardiography (focusing on patent foramen ovale or atrial septal aneurysm, with a “bubble” study added to demonstrate right-to-left shunts), Holter monitoring searching for paroxysmal arrhythmias, and hematologic studies (complete blood cell count, coagulation studies).

When this array of tests is nondiagnostic for the source of a stroke, the infarct is at least “temporarily” cryptogenic. In the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) trial,² paroxysmal atrial fibrillation (AF) was discovered in 9% of this specific cohort at 6 months, 12% at 1 year, and 30% at 3 years. If AF is not implicated, further studies may be prescribed and are considered either “advanced” or “specialized” investigations, as opposed to the contemporary standard tests.

“Advanced” evaluation is comprised of vascular studies including catheter angioplasty, transcranial Doppler ultrasonography studies looking for emboli, and investigation for occult central nervous system vasculitis. Advanced cardiac testing augments the tests enumerated above with prolonged (2-4 weeks) paroxysmal rhythm evaluations. More recently, implantable loop recorders and other devices have improved the ability to uncover occult and infrequent bouts of AF.¹

The most common cause of a right-to-left shunt is a patent foramen ovale.¹ If the shunt is responsible for a stroke, diagnosing these patients leads to treatment with antiplatelet therapy.¹ Hematologic investigative additions to a standard workup are arterial and venous hypercoagulability testing. If the workup is

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still negative after these additional efforts, “specialized” evaluations may be considered if appropriate. In this arena, genetic testing for mitochondrial diseases may be required, a detailed autoimmune evaluation may be indicated, and cerebrospinal fluid studies or even a brain biopsy may follow. Additional cardiac studies may include a cardiac MRI.

Even with the additional focused workup detailed above, there are still some embolic strokes of unknown source. The next “cryptogenic” frontier is implicating more subtle sources of emboli, including mitral annular calcium, mild left ventricular dysfunction, and aortic arch plaques. The advances in the last few years suggest there will be more of substance to come. ■

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