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# Evaluation and Management of Stroke in Young Adults

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## ABSTRACT

**Purpose of Review:** This article provides an overview of the evaluation and management of ischemic stroke in young adults, with an emphasis on cervical artery dissection, patent foramen ovale, and hypercoagulable states.

**Recent Findings:** The incidence of ischemic stroke in young patients is increasing, although the reasons remain unclear. Patients with ischemic stroke at a young age are more likely to die at an early age than their peers. Well-established vascular risk factors are prevalent in young stroke patients. Recent studies have informed the treatment of dissection and patent foramen ovale among others. The utility of testing for hypercoagulable states in ischemic stroke is unclear.

**Summary:** Ischemic stroke in young adults is a major public health problem. A wide range of etiologies of ischemic stroke is found in this age group. A careful history, thorough examination, and methodical workup are essential. Specific management is predicated on identification of the underlying etiology.

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## INTRODUCTION

Stroke is often considered a disease of older people, but an estimated 10% of patients with stroke are younger than 50 years. Recent evidence suggests that the incidence of ischemic stroke in young adults is rising,<sup>1</sup> although the reasons for that increase are unclear. These trends are especially concerning in light of recent evidence that young stroke patients are at a greatly increased risk of early death compared with the general population.<sup>2</sup> The purpose of this article is to provide an overview of some of the potential stroke etiologies to consider in patients under 50 years of age.

## STANDARD RISK FACTORS

Classic vascular risk factors, including hypertension, dyslipidemia, diabetes mellitus, and tobacco abuse are prevalent in several studies of young stroke pa-

tients. In the largest study, Finnish investigators retrospectively evaluated 1008 consecutive ischemic stroke patients aged 15 to 49 in a single university center registry from 1994 to 2007. Conventional risk factors for stroke were highly prevalent in this young stroke population: hypertension (39%), dyslipidemia (60%), and smoking (44%).<sup>3</sup> Investigators at a university center in the United States found similarly high rates of conventional risk factors.<sup>4</sup> Given the prevalence of conventional risk factors in young stroke patients, initial evaluation should approximate that of older stroke patients. Further evaluation may be necessary pending initial results. A suggested initial evaluation is shown in **Table 6-1**.

As **Table 6-2**<sup>5</sup> demonstrates, there are multiple potential etiologies of ischemic stroke in young adults. Of

**TABLE 6-1 Initial Evaluation of a Young Adult With Ischemic Stroke**

- ▶ Thorough history
- ▶ Physical examination
- ▶ Brain MRI with diffusion-weighted images and gradient recall echo or susceptibility-weighted imaging sequences
- ▶ Head and neck angiography (MR, CT, or conventional)
- ▶ Transesophageal echocardiography
- ▶ Continuous cardiac telemetry
- ▶ ECG
- ▶ Standard laboratory evaluation
  - Complete blood count
  - Comprehensive metabolic panel
  - Coagulation studies
  - Erythrocyte sedimentation rate/C-reactive protein
  - Fasting lipid panel
  - Urine cocaine and methamphetamine

MRI = magnetic resonance imaging; MR = magnetic resonance; CT = computed tomography; ECG = electrocardiogram.

**KEY POINTS**

- The incidence of stroke in young adults appears to be increasing.
- Stroke in young adults is associated with increased risk of early death.
- Standard vascular risk factors are prevalent in young stroke patients.

particular interest for this review are three categories especially germane to a discussion of stroke in young adults: (1) cervical artery dissections, (2) patent foramen ovale (PFO), and (3) hypercoagulable syndromes, including inherited thrombophilias and the antiphospholipid antibody syndrome.

**ARTERIAL DISSECTION**

Dissection is the separation of the structural components of the connective tissue network of the arterial wall and can occur in the carotid, vertebral, and intracranial arteries. The second most common lesion of the cervical arteries after atherosclerosis, dissection has traditionally been characterized as either spontaneous or secondary to major trauma. Several connective tissue disorders have also been associated with dissection, including vascular Ehlers-Danlos syndrome (type IV), Marfan syndrome, and osteogenesis imperfecta, among others. Although dissections account

for about 2% of all ischemic strokes,<sup>6</sup> they account for a higher proportion in young adults.<sup>3</sup> A population-based study in Olmsted County, Minnesota estimated the incidence as 1.72 per 100,000 per year for internal carotid artery dissections and 0.97 per 100,000 for vertebral artery dissections.<sup>7</sup> The peak incidence occurs in the fifth decade of life. Intracranial dissections appear to comprise approximately 10% of published dissection cases. In 13% to 16% of cases of dissection, multiple arteries are involved.<sup>8</sup> Recent analyses have noted significant differences in the clinical presentation, risk factors, and functional outcomes of internal carotid artery versus vertebral dissections.<sup>9,10</sup>

The classic teaching is that cervical artery dissections arise from an intimal tear and that blood enters the wall and forms an intramural hematoma. But the absence of a demonstrable intimal tear on some histologic examinations suggests that at least some dissections

**TABLE 6-2 Uncommon Causes of Stroke<sup>a</sup>**

► **Infectious and Inflammatory**

- Varicella-zoster virus
- Neurosyphilis
- Tuberculous meningitis
- Fungal meningitis
- Cysticercosis
- Lyme disease
- Chagas disease
- HIV
- Takayasu disease
- Behçet syndrome
- Neurosarcoidosis
- Kawasaki disease
- Buerger disease
- Vasculitis (primary angiitis of the CNS, Sjögren syndrome, Wegener granulomatosis, Churg-Strauss syndrome)
- Temporal arteritis

► **Genetic**

- Pulmonary arteriovenous malformations
- Hereditary hemorrhagic telangiectasia
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Fabry disease
- Marfan syndrome
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome
- Progeria
- Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) and other mitochondrial diseases
- Sturge-Weber disease
- Von Hippel-Lindau disease
- Neurofibromatosis
- Menkes disease
- Wyburn-Mason syndrome

► **Vascular Conditions of the Eyes, Ears, and Brain**

- Eales retinopathy
- Acute posterior multifocal placoid pigment epitheliopathy
- Susac syndrome
- Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS)
- Cogan syndrome

*Continued on next page*

**TABLE 6-2 Uncommon Causes of Stroke<sup>a</sup>** (Continued)

▶ **Systemic Disorders That Also Involve the Cerebrovascular System**

Microscopic polyangiitis and polyarteritis nodosa  
Systemic lupus erythematosus  
Rheumatoid arthritis  
Substance abuse  
Kohlmeier-Degos syndrome  
Inflammatory bowel disease  
Sweet syndrome  
Nephrotic syndrome  
Epidermal nevus syndrome  
Sneddon syndrome  
Scleroderma

▶ **Noninflammatory Disorders of the Arterial Wall**

Cervicocephalic arterial dissections  
Cerebral amyloid angiopathy  
Moyamoya disease  
Dilatative dolichoectasia  
Fibromuscular dysplasia

▶ **Thrombophilias (Table 6-3 and Table 6-4)**

▶ **Vasospasm Related**

▶ **Reversible Cerebral Vasoconstriction Syndrome**

▶ **Eclampsia**

▶ **Other**

Radiation vasculopathy  
Migrainous infarct  
Lymphomatoid granulomatosis  
Hypoperfusion  
Intravascular lymphoma  
Henoch-Schönlein purpura

<sup>a</sup> Data from Caplan LR, ed, Cambridge University Press.<sup>5</sup>

are caused by a primary intramural hematoma.<sup>11</sup> One study found outer wall abnormalities in superficial temporal arteries of dissection patients and proposed that an underlying arteriopathy affecting the media and adventitia played a crucial role in dissection pathogenesis.<sup>12</sup> Dissection is likely a multifactorial process, and both environmental and genetic risk factors have been implicated. The most important environmental risk

factor appears to be trauma. Dissection occurs commonly with major trauma but is also associated with minor trauma, such as chiropractic manipulation, coughing, and sneezing, among others.<sup>13</sup> Recent infection has also been associated with dissection. Several lines of evidence suggest a genetic contribution to dissection, including reports of familial dissection cases. Several candidate genes have been proposed, including the

**KEY POINTS**

- CT angiography and magnetic resonance angiography (MRA) have supplanted conventional angiography in the diagnosis of dissection.
- CTA appears to have some advantages over MRA in the diagnosis of dissection.

intercellular adhesion molecule 1 gene (*ICAM1*), the collagen, type III, alpha 1 gene (*COL3A1*), and the methylenetetrahydrofolate reductase (NAD[P]H) gene (*MTHFR*). The Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) consortium is actively investigating these and other genes as well as gene-environment interactions.<sup>8</sup>

Clinical manifestations of cervical artery dissections include both local signs and symptoms and ischemic events. Local manifestations of internal carotid artery dissections include Horner syndrome (ipsilateral), neck pain, headache, tinnitus, facial pain, and cranial nerve palsies (IX to XII most commonly). Local manifestations in vertebral dissections include posterior headache or neck pain, cervical root involvement (most commonly C5-C6 level), and lower brainstem compression (in intracranial vertebral dissection). Ischemic manifestations of internal carotid artery dissection include stroke (most commonly in the middle cerebral artery distribution), amaurosis fugax, ischemic optic neuropathy, and retinal infarction. Ischemic manifestations in vertebral

dissection include posterior circulation strokes, subarachnoid hemorrhage (in intracranial vertebral artery dissection), and spinal cord ischemia. Internal carotid artery or vertebral artery dissections resulting in arterial occlusion or stenosis are more likely to result in ischemic manifestations, while local manifestations are more likely to occur in the absence of luminal narrowing.<sup>14</sup> **Case 6-1** illustrates a common presentation of a young adult with carotid dissection.

Conventional angiography, the diagnostic mainstay of cervicocephalic dissection for many years, has now been largely replaced by noninvasive means such as CT angiography (CTA) and MR angiography (MRA). Conventional angiography is limited both by its invasiveness and its inability to visualize intramural hematoma. The luminal contour can also at times appear normal on conventional angiography. MRA can be combined with axial T1-weighted cervical MRI with fat suppression to better identify small intramural hematomas and does not require radiation. CTA, on the other hand, might be superior to MRA with

**Case 6-1**

A 34-year-old man presented with a right posterior headache, neck pain, and left-sided weakness that he noted when he awakened in the morning. He had recently started a yoga routine. He had no prior significant medical history, although he was a smoker. General examination was unremarkable. Neurologic examination was remarkable for a mild left hemiparesis. Brain MRI demonstrated restricted diffusion in the right middle cerebral artery distribution. CT angiography of the head and neck demonstrated dissection of the right internal carotid artery. Echocardiography was unremarkable. The patient was started on a heparin drip and warfarin 5 mg daily. A follow-up CT angiogram at 3 months showed resolution of the dissection, and anticoagulation was transitioned to aspirin 325 mg daily. He has had no further complications in 5 years of follow-up.

**Comment.** This patient sustained a right middle cerebral artery stroke due to dissection apparently related to minor trauma. Both his arterial healing time and the absence of recurrence are common in carotid artery dissection.

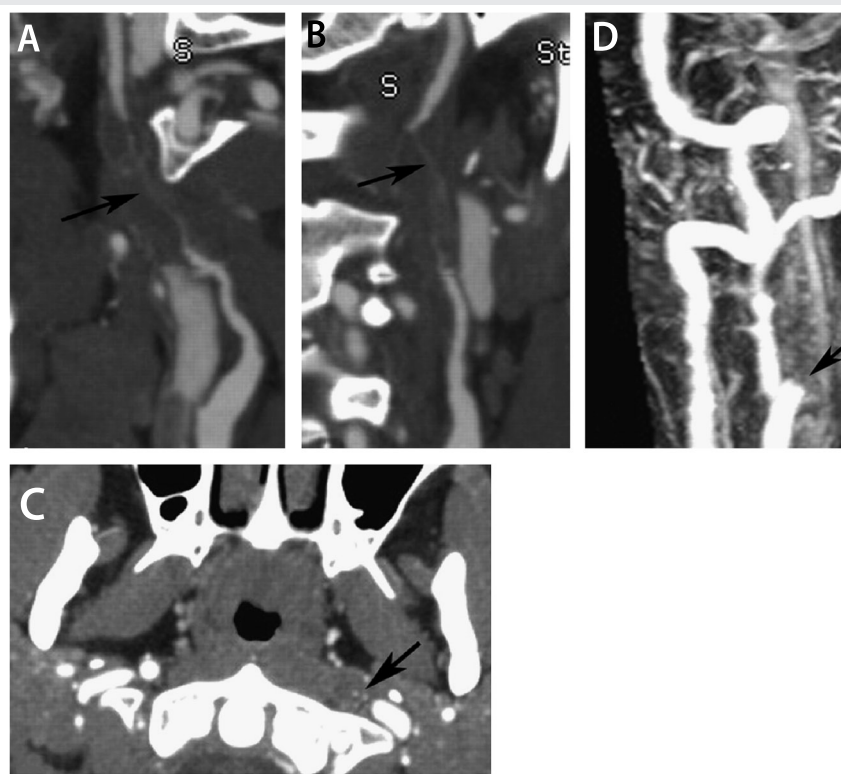
regard to diagnosis of intimal flaps, pseudoaneurysms, and high-grade stenosis<sup>15</sup> in addition to superior identification of vertebral artery dissections. **Figure 6-1** demonstrates the superiority of CTA in the setting of high-grade stenosis. High-resolution 3-tesla MRI is also emerging as a potential tool for detection of cervicocephalic dissection and delineation of intramural thrombus versus intraluminal thrombus.<sup>16</sup>

The treatment of cervicocephalic dissections is controversial owing to a lack of randomized controlled trials. In the hyperacute setting, there is no clear contraindication to thrombolysis.

A recent meta-analysis found that thrombolysis in patients with stroke related to dissection had similar safety and outcome profiles compared with patients with strokes unrelated to dissection,<sup>17</sup> although other studies have questioned the efficacy of thrombolysis for dissection.<sup>18</sup> Patients are commonly prescribed anticoagulants given concerns about recurrent events. A common practice is to initiate an anticoagulant in the acute setting and then to repeat angiography in 3 months. If the dissection has resolved, the patient is typically transitioned to an antiplatelet agent.

#### KEY POINT

- There is no contraindication to tissue plasminogen activator in strokes due to dissection.



**FIGURE 6-1** Example of a long-segment high-grade stenosis (string sign) from dissection identified on CT angiography (CTA), which appeared occluded on MRI/magnetic resonance angiography (MRA). *A, B*, Curved planar reformatted images of the left internal carotid artery demonstrate flamelike tapering of the proximal vessel with wall thickening and long-segment high-grade stenosis (*arrow*). *C*, Axial plane from CTA shows the tiny residual lumen of the vessel (*arrow*). *D*, Contrast-enhanced MRA acquired on the same day demonstrates apparent occlusion just distal to the carotid bifurcation (*arrow*).

Modified with permission from Vertinsky AT, et al, *AJNR Am J Neuroradiol.* <sup>15</sup> © 2008 American Society of Neuroradiology. [www.ajnr.org/content/29/9/1753.long](http://www.ajnr.org/content/29/9/1753.long).



If irregularities persist, anticoagulation is generally continued until the arterial dissection resolves, completely occludes, or stabilizes, at which time an antiplatelet agent is initiated. Recent work, however, has questioned whether this approach is warranted. A large nonrandomized study found that ischemic recurrence rates were very low both in patients treated with antiplatelet agents and those treated with anticoagulants.<sup>19</sup> An ongoing randomized clinical trial compares antiplatelet agents and anticoagulation in acute dissection<sup>20</sup>; the nonrandomized portion of this study found no evidence of superiority for anticoagulation.<sup>21</sup>

Recurrence rates of both ischemic events and dissections are generally reported as low. One-year ischemic recurrence rates range from 0% to 13%,<sup>8</sup> and recurrences generally occur in the first few weeks following initial presentation. Dissection recurrence rates are low in population-based studies.<sup>7</sup> Academic centers report higher rates but may be subject to referral bias.<sup>8</sup>

### **PATENT FORAMEN OVALE**

PFO, an embryonic defect in the atrial septum, has been postulated as a source for paradoxical embolism for decades. The proportion of the general population with PFO is approximately 20%, but in young stroke patients this proportion is about 50%. Co-occurrence with atrial septal aneurysm (greater than 10-mm septal excursion during a cardiac cycle) seems to confer additional risk.<sup>22,23</sup> The presence of PFO in the setting of an inherited or acquired thrombophilia is especially important because it provides a potential mechanism for venous material to pass into the arterial circulation (ie, paradoxical embolization). Dozens of observational studies have suggested a higher rate of recurrent stroke in medically treated pa-

tients compared with closure,<sup>24</sup> but randomized data were not available.

Three randomized controlled trials, each investigating the role of PFO for secondary stroke prevention, have now been published. The first of these, the CLOSURE-I trial, investigated the STARFlex device in patients 60 years old or younger with stroke or TIA and a PFO.<sup>25</sup> The primary end point was a composite of stroke or TIA in 2 years of follow-up, 30-day all-cause mortality, and death from neurologic cause between 31 days and 2 years. More than 900 patients were enrolled. The primary end point occurred in 5.5% of the closure group and 6.8% of the medical group (hazard ratio [HR] 0.78; 95% confidence interval [CI], 0.45 to 1.35;  $P=.37$ ). Major periprocedural complications occurred in 13 (3.2%) patients in the closure group. The authors found plausible alternative explanations to a PFO-related cause for stroke or TIA in a majority of patients in both the closure and medical groups.

The PC trial investigated a different device, the Amplatzer PFO occluder, in patients younger than 60 years with stroke, TIA, or peripheral thromboembolic event who had a PFO.<sup>26</sup> More than 400 patients were enrolled. The primary end point (a composite of non-fatal stroke, TIA, peripheral embolism, and death) occurred in 3.4% of the closure group and 5.2% of the medical group (HR 0.63; 95% CI, 0.24 to 1.62;  $P=.34$ ). The authors reported three (1.5%) minor procedural complications in the closure group.

The Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial was published concurrently with the PC trial and also investigated the PFO Amplatzer occluder.<sup>27</sup> The investigators enrolled nearly 1000 patients with

cryptogenic strokes and PFO. The primary end point was a composite of nonfatal and fatal ischemic stroke and early death. Nine patients with recurrent stroke were in the closure group and 16 in the medical group (HR 0.49; 95% CI, 0.22 to 1.11;  $P=.08$ ). Procedure-related adverse events occurred in 21 (4.2%) patients in the closure group.

Taken individually, these trials did not demonstrate the superiority of PFO closure over medical management; however, a recent meta-analysis of the trials suggests potential benefit.<sup>28</sup> Given the relatively large statistical effect sizes in the trials, further studies are likely forthcoming in an attempt to identify the patient population most likely to benefit.

The optimal management of cryptogenic stroke in a young person with PFO remains unclear at this point. Given the negative trial data, for now closure should be limited to the setting of a clinical trial. The optimal long-term antithrombotic agent for the stroke patient with PFO is also unclear. No specific guidelines have been developed for the co-occurrence of PFO and atrial septal aneurysm. Given the lack of definitive data, the decision regarding antiplatelet versus anticoagulant therapy should be informed by patient risk stratification and risk tolerance, although in the absence of a deep vein thrombosis or known hypercoagulable state antiplatelet therapy is typically recommended. Modifiable risk factors should be aggressively addressed.

## **HYPERCOAGULABLE CAUSES OF STROKE**

Up to 4% of ischemic strokes are thought to be due to coagulation disorders, and young patients in particular are often screened for hypercoagulable syndromes. Hypercoagulable syndromes may include inherited deficiencies and acquired conditions. The coagulation

cascade is a complex system with multiple sites in which alteration could result in thrombophilia.

Several conditions are purported to predispose patients to thromboembolism and, by extension, acute ischemic stroke. Most of these conditions are primarily associated with venous thrombosis, although a few conditions such as homocystinuria and antiphospholipid antibody syndrome are associated with arterial thrombosis. The presumed mechanism for arterial stroke in a patient with a venous thrombophilia is paradoxical embolus, most commonly through a PFO. A pressure gradient promoting passage of venous material to the arterial circulation may be generated via the Valsalva maneuver. The inherited thrombophilias with the best-established evidence base for venous thromboembolism are factor V Leiden and activated protein C resistance, prothrombin gene mutation, protein S deficiency, protein C deficiency, and antithrombin III deficiency. The most common acquired thrombophilia is antiphospholipid antibody syndrome. **Table 6-3**<sup>29</sup> and **Table 6-4**<sup>29</sup> list the most common inherited and acquired thrombophilic states, respectively.

### **Factor V Leiden**

Approximately 90% to 95% of patients with activated protein C resistance have the identical mutation, which is a single point mutation in the factor V gene (factor V R506Q). Factor V Leiden increases the risk of thrombosis by increasing thrombin production. Factor V Leiden is by far the most common genetic risk factor for thrombophilia. The prevalence of factor V Leiden heterozygosity varies within American populations; the frequency is 5.3% in whites, 2.2% in Hispanics, 1.3% in Native Americans, 1.2% in African Americans, and 0.5% in Asian Americans.<sup>30</sup> Factor V Leiden is not fully penetrant, and only

### **KEY POINTS**

- Patent foramen ovale closure trials have yet to demonstrate superiority over medical management.
- The best long-term antithrombotic agent for stroke patients with patent foramen ovale remains unclear.
- The thrombophilias with the best evidence for venous thromboembolism are factor V Leiden, prothrombin gene mutation, protein S deficiency, protein C deficiency, and antithrombin III deficiency.



**TABLE 6-3 Primary/Inherited Hypercoagulable States<sup>a</sup>**

- ▶ Factor V Leiden mutation/activated protein C resistance
- ▶ Prothrombin *G20210A* mutation
- ▶ Protein S deficiency
- ▶ Protein C deficiency
- ▶ Antithrombin deficiency
- ▶ Heparin cofactor II deficiency
- ▶ Fibrinogen disorders
- ▶ Elevated thrombin-activatable fibrinolysis inhibitor
- ▶ Elevated factor VIII
- ▶ Elevated factor IX
- ▶ Elevated factor XI
- ▶ Fibrinolytic system disorders
- ▶ Methylene tetrahydrofolate reductase (NAD[P]H) (*MTHFR*) gene mutation

<sup>a</sup> Modified with permission from Biller J, ed, Saunders.<sup>29</sup> © 2009 Elsevier.

5% to 10% of factor V Leiden heterozygotes will experience a symptomatic venous thromboembolic event. Homozygotes are much rarer but have a markedly elevated thrombotic risk (the relative risk for first episode of venous thrombosis is 7 in heterozygotes and 80 in homozygotes).<sup>31</sup> Activated protein C resistance is associated with several other factors, including elevated factor VIII levels, oral contraceptives, pregnancy, hormone replacement, cancer, antiphospholipid antibody syndrome, and smoking. Patients with factor V Leiden frequently have other thrombophilias,<sup>32-34</sup> and these patients appear to be at increased risk for thrombosis. Factor V Leiden has not been convincingly linked to arterial thrombosis. **Case 6-2** is a typical example of a patient with factor V Leiden.

### Prothrombin Gene Mutation

Prothrombin deficiency is the second most common inherited thrombophilia after factor V Leiden, and the source of the thrombophilia is a single point mutation (*G20210A*). Carriers have higher prothrombin levels and are at higher

risk of thrombosis. Prevalence of the mutation varies in populations; up to 7% of the white population carries the mutation, while it is very rare in black or Asian populations.<sup>36</sup> Homozygotes are at increased risk for DVT and cerebral venous sinus thrombosis, especially in patients taking oral contraceptives. Conclusive evidence of increased risk for arterial thrombosis in patients with prothrombin deficiency has not been established.

### Protein S Deficiency

Protein S is a vitamin K-dependent protein that enhances fibrinolysis, inhibits prothrombin activation, and reduces thrombin production. Protein S circulates in both free and protein-bound forms. Deficiencies of protein S can be genetic or acquired. In genetic cases, inheritance is predominantly autosomal dominant. Heterozygotes are at risk for recurrent venous thromboembolism; homozygous protein S deficiency is usually incompatible with life. Acquired protein S deficiency is associated with pregnancy, oral contraceptive pill use, disseminated

**TABLE 6-4** Secondary/Acquired Hypercoagulable States<sup>a</sup>

- ▶ Antiphospholipid syndrome
- ▶ Protein S deficiency
- ▶ Protein C deficiency
- ▶ Antithrombin deficiency
- ▶ Myeloproliferative disorders
- ▶ Paraproteinemia
- ▶ Cancer
- ▶ Pregnancy
- ▶ Oral contraceptives
- ▶ Polycythemia rubra vera
- ▶ Iron deficiency anemia
- ▶ Hemoglobinopathies
- ▶ Sickle cell disease
- ▶ Thalassemia
- ▶ Platelet disorders
- ▶ Essential thrombocythemia
- ▶ Heparin-induced thrombocytopenia
- ▶ Thrombotic thrombocytopenic purpura
- ▶ Homocystinuria
- ▶ Hyperhomocysteinemia
- ▶ Paroxysmal nocturnal hemoglobinuria
- ▶ Diabetes mellitus
- ▶ Ovarian hyperstimulation syndrome
- ▶ Nephrotic syndrome
- ▶ Disseminated intravascular coagulation
- ▶ Plasma glutathione peroxidase deficiency

<sup>a</sup> Modified with permission from Biller J, ed, Saunders.<sup>29</sup> © 2009 Elsevier.

intravascular coagulation, HIV, nephrotic syndrome, systemic lupus erythematosus (SLE), liver disease, and asparaginase therapy. Protein S deficiency has not been convincingly linked to arterial thrombosis.

### Protein C Deficiency

Activated protein C inactivates factors Va and VIIIa, which are important for

thrombin generation. Protein C deficiency can be either genetic or acquired. Heterozygosity occurs in 0.2% to 0.5% of the general population. Acquired protein C deficiency is associated with severe infection (especially meningococcemia), liver disease, disseminated intravascular coagulation, acute respiratory distress syndrome, sepsis, and several medications, including methotrexate, 5-fluorouracil, and cyclophosphamide. A convincing link to arterial thrombosis has not been demonstrated.

### Antithrombin Deficiency

Antithrombin (formerly called antithrombin III) is an inhibitor of thrombin. Antithrombin deficiency can be both genetic and acquired. The inheritance pattern is usually autosomal dominant. The prevalence in the general population may be 1 in 500. Acquired antithrombin deficiency is associated with disseminated intravascular coagulation, sepsis, liver disease, nephrotic syndrome, oral contraceptives, estrogen, and asparaginase. Patients with antithrombin deficiency appear to be at no increased risk for arterial thrombosis.

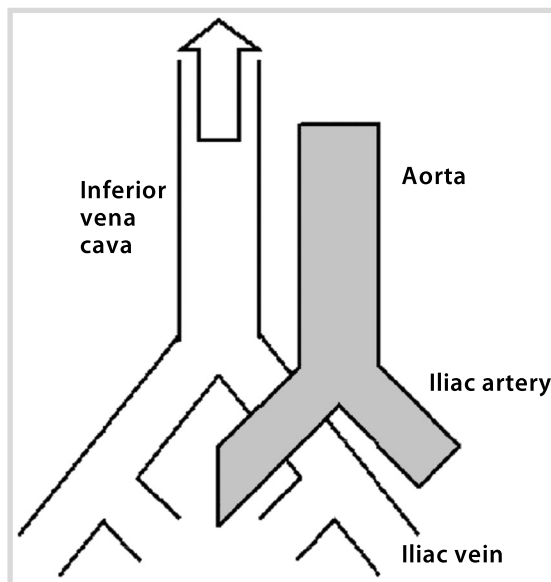
### Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome (APS) is an autoimmune condition associated with both venous and arterial thrombosis. APS often but not always occurs with SLE. The most common thrombotic event in patients with APS is DVT; stroke is the most common arterial event. The diagnostic criteria for APS are found in **Table 6-5**<sup>37</sup>. Any patient with rheumatologic disease and stroke should be screened for APS; it may also be reasonable to screen any patient with stroke younger than age 45 for APS.<sup>38</sup> Treatment generally consists of long-term anticoagulation. **Case 6-3** is an example of SLE-associated

**Case 6-2**

A 42-year-old woman without a significant prior medical history presented with a 2-day history of difficulty seeing to the left. She did not take oral contraceptives, smoke, or use illicit drugs. She had one previous miscarriage but no history of deep venous thromboses (DVTs), pulmonary emboli, or other bleeding or clotting issues. She did, however, have a strong family history of factor V Leiden mutation in her mother and brother, and her maternal grandmother died of blood clots. Neurologic examination demonstrated a left homonymous hemianopia. Brain MRI demonstrated restricted diffusion in the right occipital lobe. CT angiography of the head and neck was unremarkable. Transesophageal echocardiography demonstrated a small right-to-left shunt via foramen ovale on the saline contrast study, and an atrial septal aneurysm. She was heterozygous for the factor V Leiden mutation. The remainder of her hypercoagulable workup was unremarkable. Lower extremity Doppler ultrasound demonstrated no DVT in the legs. Magnetic resonance venography of the pelvis demonstrated DVT in the left common iliac vein due to May-Thurner syndrome. She was initially treated with aspirin 325 mg/d and then transitioned to anticoagulation with warfarin.

**Comment.** This case emphasizes the importance of a methodical approach in cryptogenic stroke. A strong family history prompted an investigation into thrombophilia, transesophageal echocardiography demonstrated a shunt, and further evaluation yielded a venous source. May-Thurner syndrome (iliocaval compression) (Figure 6-2<sup>35</sup>) is an important consideration in the setting of cryptogenic stroke, thrombophilia, and patent foramen ovale.

**FIGURE 6-2**

Anatomic diagram of May-Thurner syndrome with the right common iliac artery overlying the left common iliac vein. Iliocaval compression can lead to thrombus formation.

Reprinted with permission from Kiernan TJ, et al, *Stroke*.<sup>35</sup> © 2009 American Heart Association. [stroke.ahajournals.org/content/40/4/1502.long](http://stroke.ahajournals.org/content/40/4/1502.long).

APS manifesting with multiple posterior circulation strokes.

Catastrophic antiphospholipid antibody syndrome occurs in a small subset of patients with antiphospholipid

antibody syndrome and is characterized by three or more new organ thromboses within 1 week. Definitive diagnosis requires demonstration of microthrombus on biopsy.<sup>39</sup> Treatment of catastrophic

**TABLE 6-5 Revised Classification Criteria for the Antiphospholipid Syndrome<sup>a</sup>**

**Clinical Criteria**

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ. Thrombosis must be confirmed via imaging, Doppler studies, or histopathology, with the exception of superficial venous thrombosis.

2. Pregnancy morbidity

- a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasound or examination, or
- b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of preeclampsia or severe placental insufficiency, or
- c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and exclusion of paternal and maternal chromosomal causes.

**Laboratory Criteria**

- 1. Anticardiolipin antibody of IgG and/or IgM isotype and measured by a standardized enzyme-linked immunoabsorbent assay or anti- $\beta$ 2-glycoprotein 1 of IgG and/or IgM isotype in blood, present in medium or high titer, on two or more occasions 12 weeks or more apart.
- 2. Lupus anticoagulant present in plasma on two or more occasions 12 weeks or more apart and detected according to the guidelines of the International Society on Thrombosis and Haemostasis in the following steps:
  - a. Demonstration of a prolonged phospholipid-dependent coagulation screening test, eg, activated partial thromboplastin time, Kaolin clotting time, dilute Russell viper venom time, dilute Prothrombin time, Textarin time.
  - b. Failure to correct the prolonged screening test by mixing with normal platelet-poor plasma.
  - c. Shortening or correction of the prolonged screening test by the addition of excess phospholipid.
  - d. Exclusion of other coagulopathies as appropriate, eg, factor VIII inhibitor, heparin.

IgG = immunoglobulin G; IgM = immunoglobulin M.

<sup>a</sup> Modified from Miyakis S, et al, *J Thromb Haemost*.<sup>37</sup> © 2006, John Wiley & Sons, Inc. [onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2006.01753.x/full](http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2006.01753.x/full).

antiphospholipid antibody syndrome includes treatment of any underlying predisposing condition, heparin, and steroids, with the addition of plasma exchange if warranted.<sup>40</sup>

**Diagnostic Approach**

Factor V Leiden diagnostic testing includes functional activated protein C assays or direct mutation testing via PCR. Prothrombin mutation is diagnosed via *G20210A* PCR testing. The

reliability of nongenetic tests for protein S, protein C, and antithrombin deficiency depends on the clinical scenario. Definitive diagnosis can be challenging given testing limitations, timing considerations in the acute phase, and potential confounding due to medications (especially anticoagulants). For protein S deficiency, both free and total protein S antigen and functional protein S assays are commonly used. The diagnosis of protein C deficiency is made somewhat

**KEY POINT**

■ Studies have not demonstrated a convincing association between hypercoagulable states and ischemic stroke.

**Case 6-3**

A 24-year-old woman with systemic lupus erythematosus (SLE) and a history of migraine headaches presented with headache and difficulty walking. Neurologic examination was remarkable for somnolence, dysarthria, and a central right facial droop. No focal weakness or dystaxia was noted. Brain MRI demonstrated acute infarcts in the bilateral cerebellar hemispheres, the bilateral pons, and the left thalamus. CT angiogram of the head and neck demonstrated diminished flow in the right vertebral artery and occlusion or near occlusion of the distal basilar artery but no dissection. Transesophageal echocardiography showed no left atrial appendage abnormality, valvular abnormality, or right-to-left shunt. Anticardiolipin and anti- $\beta_2$ -glycoprotein titers were markedly elevated. Antiphospholipid antibody syndrome was suspected. She was started by a rheumatologist on steroids, rituximab, and an antiplatelet agent (aspirin 325 mg/d) initially and was subsequently transitioned to anticoagulation (warfarin). Follow-up studies 4 months after the initial event confirmed the diagnosis of antiphospholipid antibody syndrome.

**Comment.** The presumed mechanism of stroke in this young woman was antiphospholipid antibody syndrome associated with SLE. Antiphospholipid antibody syndrome can affect both the venous and arterial circulations, and the most common arterial manifestation is ischemic stroke.

difficult by the wide range of normal values in the population. Normal protein C antigen ranges from 70% to 140% of normal; levels less than 55% are likely due to a genetic abnormality. Protein C functional levels are the preferred screening test. Antithrombin deficiency is diagnosed using the antithrombin-heparin cofactor assay.

A reasonable approach for protein S, protein C, and antithrombin deficiency testing would be to repeat studies a few months after the stroke (and with the patient off anticoagulants for at least 2 weeks) before committing the patient to long-term anticoagulation. Interpretation can be challenging. One study found that approximately 30% of testing for hypercoagulable states in routine academic practice was performed in settings in which the results were not interpretable.<sup>41</sup> Another study found that nearly 75% of the diagnosed thrombophilias were subsequently not confirmed on follow-up testing.<sup>42</sup>

Even if a thrombophilia is reliably identified, it is unclear whether the

thrombophilia is associated with an increased risk for ischemic stroke. An extensive review<sup>43</sup> identified six case-control studies of 50 or more ischemic stroke cases with protein S deficiency, protein C deficiency, and/or antithrombin deficiency. In four of the six studies, the proportion of cases with the deficiency was greater than that of the controls, but this difference was not statistically significant in any of the studies (Table 6-6). One of these studies also stratified by presumed mechanism and inherited thrombophilia and did not find significant differences.<sup>44</sup> This review also identified 16 case-control studies of 50 or more cases of factor V Leiden or prothrombin mutation. Fourteen of these studies found no statistical difference between the cases and controls with regard to factor V Leiden or prothrombin mutation (Table 6-7). The authors of that review also reviewed nine case-control studies (without limiting the number of cases) that evaluated the relationship between PFO, ischemic

**TABLE 6-6 Case-Control Studies of Protein C Deficiency, Protein S Deficiency, and Antithrombin Deficiency in Patients With Ischemic Stroke<sup>a</sup>**

Reference	Age	Number of Cases and Controls	Thrombophilia Tested	% Identified in Cases	% Identified in Controls	Statistical Significance
Sastry et al, 2006	16–39	101 101	PC, PS, AT	7.9	8.9	NS
Jerrard-Dunne et al, 2003	≤65	130 130	PC, PS, AT	8.5 <sup>b</sup>	6.3 <sup>b</sup>	NS
Hankey et al, 2001	Mean 66	219 205	PC, PS, AT	7.3	6.8	NS
Maragaglione et al, 1999	3–50	202 1036	PC, PS, AT	0	0	NS
De Stefano et al, 1998	2–50	72 198	PC, PS, AT	1.4	0	NS
Mayer et al, 1993	>39	94 94	PS	21	20	NS

PC = protein C deficiency; PS = protein S deficiency; AT = antithrombin deficiency; NS = not significant.

<sup>a</sup> Reprinted with permission from Morris et al, *Stroke*.<sup>43</sup> © 2010 American Heart Association. [stroke.ahajournals.org/content/41/12/2985.long](http://stroke.ahajournals.org/content/41/12/2985.long).

<sup>b</sup> Using ethnicity-specific reference ranges.

stroke, and inherited thrombophilias. None of the studies that evaluated protein C, protein S, or antithrombin deficiency found an association with PFO and stroke. The studies were mixed with regard to factor V Leiden and prothrombin mutation, with a few demonstrating a significant association.<sup>43</sup>

Most experts recommend a tailored approach to testing for hypercoagulable states, in which high-risk individuals (ie, younger, undetermined cause of stroke, history of venous thrombosis, multiple miscarriages, frequent thrombotic recurrences, family history of venous thromboembolic disease, etc) are selected for testing.<sup>45</sup> Testing for factor V Leiden and prothrombin *G20210A* in nonwhite populations is likely to be very low-yield, given the very low prevalence of the mutations in these populations. A suggested approach to testing for thrombophilic states is shown in **Table 6-8**. In the absence of a right-to-left shunt, testing for thrombophilias (other than possibly

antiphospholipid antibody syndrome) seems low yield. Young adults with stroke and a right-to-left shunt should be evaluated for deep venous thrombosis with compression ultrasonography of the lower extremities and venography of the pelvis.

### Treatment

The best treatment regimen for most hypercoagulable states is unknown, and few large studies to direct treatment decisions are available. One exception is the Antiphospholipid Antibodies in Stroke Study/Warfarin-Aspirin Recurrent Stroke Study collaboration, which compared warfarin and aspirin for prevention of recurrent stroke in patients with antiphospholipid antibodies and found no statistical difference in outcomes.<sup>46</sup>

Many clinicians use long-term anticoagulation for patients with inherited coagulation disorders. The optimal duration of treatment is unclear. Whether the

### KEY POINT

- Young adults with stroke and a right-to-left shunt should be evaluated for deep venous thrombosis with compression ultrasonography of the lower extremities and venography of the pelvis.



**TABLE 6-7** Case Control Studies of Factor V Leiden and Prothrombin Mutation in Young Patients (Younger Than 60 Years) With Ischemic Stroke<sup>a</sup>

Reference	Age	Number of Cases and Controls	Thrombophilia Tested	% Identified in Cases	% Identified in Controls	Statistical Significance
Sastry et al, 2006	16–39	101	FVL	4.0	7.9	NS
		101	PTM	2.0	0.0	NS
Slooter et al, 2005 <sup>b</sup>	20–49	193	FVL	7.8	5.5	OR 1.8
		767	PTM	2.7	2.4	OR 1.0
Lalouschek et al, 2005	<60	468	FVL	6.2	6.4	NS
		468	PTM	5.0	2.0	<i>P</i> =.032
Madonna et al, 2002	0.5–50	132	FVL	5.3	6.5	NS
		162	PTM	7.6	6.1	NS
Austin et al, 2002	18–50	67	FVL	7.4	5.1	NS
		79	PTM	4.4	2.5	NS
Lopaciuk et al, 2001	≤45	100	FVL	3.0	4.2	NS
		283	PTM	2.0	2.1	NS
Voetsch et al, 2000	15–45	153	FVL	3.3	3.6	NS
		225	PTM	4.6	2.2	NS
Maragaglione et al, 1999	3–50	202	FVL	19.6	4.2	<i>P</i> <.0001
		1036	PTM	5.0	4.2	NS
De Stefano et al, 1998	2–50	72	FVL	5.5	2.5	NS
		198	PTM	12.5	2.5	<i>P</i> =.0001
Nabavi et al, 1998	15–45	225	FVL	8.4	6.0	NS
		200				
Longstreth et al, 1998 <sup>b</sup>	18–44	106	FVL	0.9	4.1	NS
		391	PTM	1.9	1.6	NS
Bentolila et al, 1997	18–49	125	FVL	6.7	5.9	NS
		134	PTM	6.4	3.7	NS
Martinelli et al, 1997	43 ± 13	155	FVL	3.2	1.3	NS
		155	PTM	3.8	3.2	NS
Sanchez et al, 1997	6–52	66	FVL	4.5	4.5	NS
Landi et al, 1996	5–44	95	FVL	4.2	1.6	NS
		190				
Kontula et al, 1995	<60	236	FVL	4.5	2.9	NS
		137				

FVL = Factor V Leiden; PTM = prothrombin mutation; NS = not significant; OR = odds ratio.

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<sup>b</sup> Only women were included in this study.

cost-benefit ratio is favorable over the long term for ischemic stroke patients identified with thrombophilias is also unclear. For acquired thrombophilias, therapy is targeted toward the specific predisposing condition. Many experts recommend discontinuing oral contraceptives and hormones in patients with

thrombophilia. Smoking cessation is essential.

**SUMMARY**

The incidence of ischemic stroke in young adults is increasing. The list of potential stroke etiologies is extensive, and a thorough history, examination,

**TABLE 6-8 Thrombophilia Screening Panel**

- ▶ Factor V Leiden mutation PCR or activated protein C resistance (low yield in nonwhite populations)
- ▶ Prothrombin *G20210A* mutation (low yield in nonwhite populations)
- ▶ Protein S functional, protein S antigen—total and free
- ▶ Protein C functional
- ▶ Antithrombin: antithrombin-heparin cofactor assay
- ▶ Anticardiolipin antibodies (IgG and IgM)
- ▶ Lupus anticoagulant (dilute Russell viper venom time, kaolin, etc)
- ▶  $\beta_2$ -Glycoprotein 1 antibodies (IgG and IgM)
- ▶ Additional considerations
  - Methylenetetrahydrofolate reductase (NAD[P]H) (*MTHFR*) mutation
  - Homocysteine level
  - Factor VIII level
  - Fibrinogen testing

and tailored workup are essential. Cervical artery dissection, PFO, and thrombophilias are potential causes of stroke in young adults.

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