Although rare, Takayasu arteritis should be sought in unusual presentations of stroke, especially in women in early adulthood.

By Harold P. Adams Jr., MD

Etiology and Pathophysiology
Takayasu arteritis (TA) is a rare inflammatory vasculopathy preferentially affecting the aorta and its major branches and is a potential cause of stroke in young adults. Although the precise etiology of TA is unknown, it may be triggered by an infectious process. The course of TA is mediated by T cells, macrophages, and dendritic cells in the arterial wall. Elevated interleukin-6 and tissue necrosis factor-α (TNF-α) levels are correlated with disease activity. A potential genetic relationship with the HLA-B*52 allele, which is more prevalent in Asian populations, has been reported. The initial sites for the lesions of TA are the aortic annulus and the origin of the great arteries from the aortic arch. The inflammatory process, marked by clusters of macrophages with or without giant cells, starts in the medial and adventitial layers before becoming panarteritis. The aortitis eventually leads to extensive fibrosis and increases arterial wall thickness. Subsequently, an aortic aneurysm, aortic valve disease, and extensive disease of the extracranial vasculature may develop. Although some of the pathologic findings overlap with those seen in people with giant cell arteritis who have aortic involvement, giant cell arteritis differs epidemiologically; it more commonly affects persons more than age 60.

Epidemiology
The epidemiologic features of TA include the early age of onset and high prevalence among women and Asians, with diagnosis after age 40 rare. Most case series report that approximately 90% of people affected are women with mean age 26. The presentations of TA differ in men, who have more involvement of the abdominal aorta compared with women, who have primarily aortic arch involvement. The pattern of TA also differs among ethnic groups with aortic arch disease more common in people of Japanese or European descent compared with people of South Asian descent who more commonly have abdominal aortic and renal artery disease. The pattern of disease in the US is similar to that seen in Europe, and the epidemiology of TA in the US reflects the ethnic diversity of the US population.

Clinical Presentation
The course of TA evolves over years and is highly variable. In the initial phase of the disorder, symptoms consist of nonspecific complaints (eg, low back pain, arthritis, myalgias, weight loss, night sweats, or low-grade fever). Subsequently, some develop pain in the carotid area of the neck or chest pain reflecting carotid or aortic disease. A neurologist may see a person with symptoms of carotidynia and evidence of Horner syndrome. The third phase of TA features the classic features of end-organ ischemia such as limb claudication, seizures, syncope, vertigo, and stroke. Angina, myocardial infarction, or visual loss may also be present. Because of the vague nature of the early disease manifestations, most people are not diagnosed until complications—including stroke—have occurred. In a study of 52 participants with TA in Canada, 15 had severe ischemic events, including 5 with stroke. These events generally occurred before or at the time of the TA diagnosis.

Findings on physical examination include hypertension, loss or inequality of pulses in the upper extremities, asymmetric blood pressures between the upper extremities, or bruits heard over the neck and supraclavicular region. The loss of palpable pulses in the upper extremities gives rise to another name for TA—pulseless disease. Differences between blood pressures and pulses in the 2 upper extremities are more commonly found among women whereas men are more likely to be hypertensive. If there is subclavian and axillary artery involvement, blood pressure measurements may be unreliable and need to be assessed in the legs. A pulsatile enlargement of the aorta may be detected on abdominal examination in an individual with an aneurysm (this scenario is more common in men). Because of the lower incidence of TA in men and presentation without what are considered more classic symptoms, men often have delays in diagnosis.

Childhood Presentation
Children, including infants, may develop TA; it is among the most common vasculitides in childhood. The mean age of children with TA is 12 to 14 years. In a retrospective study comparing 29 children and 48 adults with TA, the relationship to the female sex was less strong, the duration of symptoms was shorter, and there was a higher rate of renal
involvement with hypertension among children. The other features of TA in children are similar to those in adults. Stroke affects approximately 5% to 15% of people with TA. Although stroke occurs late in the course of TA, it is often the presenting symptom, such that a neurologist may be the first physician to confront a case. Variable patterns and locations of stroke occur in both the carotid and vertebrobasilar circulations and may be secondary to either intracranial or extracranial disease. Most cases of stroke appear to be secondary to hypoperfusion. Visual symptoms, most commonly bilateral vision loss—the most frequent complaints—are associated with vertebral artery involvement. Retinal involvement secondary to carotid disease also occurs. On examination, carotid artery tenderness (carotidynia), cervical bruits, and differences in peripheral pulses and blood pressures are features that point to TA as a cause of a new stroke. Brain imaging findings of small- to medium-sized strokes in the cortex or subcortical structures in multiple vascular territories also suggest TA.

**Diagnostic Testing and Diagnosis**

**Laboratory Tests**

Acute phase reactants, or inflammatory markers, may be elevated early in the disease but may normalize later, which is the time when neurologic symptoms usually develop. In general, laboratory investigations are not very helpful. The erythrocyte sedimentation rate (ESR) is more likely to be elevated than the C-reactive protein (CRP) level. Elevations in platelet and white blood cells counts, abnormal renal function tests, and mild anemia may be found. The absence of elevated inflammatory markers does not exclude the diagnosis of TA and changes in their levels cannot be used to monitor responses to therapy.

**Imaging Studies**

Vascular imaging is the key diagnostic test and is used to monitor the course of the disease. Different imaging modalities have different advantages and disadvantages such that the choice of imaging studies is individualized (Table 1). In the past, digital subtraction angiography (DSA) was the standard imaging study but the invasive nature of the test and its inability to assess the arterial wall limit its use in therapeutic procedures. Information about the status of the arterial wall, including gadolinium enhancement suggestive of inflammation, and the development of both extracranial and intracranial vascular lesions can be achieved with MRI and magnetic resonance angiography (MRA). To differentiate arterial narrowing secondary to TA from atherosclerosis, CT and CT angiography (CTA) are helpful. The appearance of a double ring in the arterial wall following contrast points to TA. The combination of CT and positron emission tomography (PET) is useful in assessing the activity of the vasculitis.

### TABLE 1. VASCULAR IMAGING OPTIONS FOR TAKAYASU ARTERITIS

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<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| DSA      | • Defines arterial lumen (occlusion, stenosis, dissection, aneurysm)  
• Can evaluate intracranial and extracranial vasculature  
• Often combined with endovascular intervention | • Invasive procedure with potential complications  
• Gives limited information about arterial wall |
| MRI and MRA | • Noninvasive studies that do not involve radiation exposure  
• May assess both arterial lumen and wall  
• May detect aneurysm or dissection of aorta  
• Provides information about the size and location of strokes  
• Contrast enhanced studies may show inflammation  
• May be done repetitively to monitor disease | • May not be performed in patients with ferromagnetic devices or metal in the body (some MRI compatible pacemakers)  
• In renal failure, gadolinium contrast, which is necessary for imaging of neck and chest  
• Long acquisition time and claustrophobia |
| CT and CTA | • Noninvasive studies that can assess both arterial lumen and wall  
• May detect aneurysm or dissection of aorta  
• May provide information about stroke  
• May be done more quickly than MRI/MRA  
• May be combined with PET to assess disease activity | • Relatively large radiation exposure, particularly when combined with PET  
• Limited utility for sequential monitoring of disease |
| PET      | • Gives evidence on activity of the vasculitis  
• May be combined with CT to correlate activity and degree of artery disease | • Not widely available and expensive  
• Large radiation dosage  
• Done alone, does not assess severity of artery disease |
| Ultrasound | • Noninvasive study that has no radiation exposure  
• Repeated studies can assess for disease activity  
• May assess abdominal aorta and vessels in neck, shoulder, and axilla | • May not assess arch or thoracic aorta  
• Dependent on skills of person performing the test |

Abbreviations: CTA, CT angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; PET, positron emission tomography
emission tomography (PET) may be used to assess vascular wall inflammation, although this combination is costly and involves large radiation exposure. Ultrasonography may detect intima-media thickness, stenosis, or occlusion of the vertebral, carotid, axillary, and subclavian arteries and abdominal aorta. Concentric thickening of the wall, which is often bright, may be caused by inflammation or edema.

Prognosis

Overall, the course of TA appears to be less ominous than previously thought. Approximately 20% of patients have a self-limited disease. For the remainder, the typical course is a slow progression with relapses. The risk of ischemic complications appears higher in men compared with women. Prognosis is influenced by the type and extent of arterial complications, including stroke, myocardial ischemia, limb ischemia, hypertension, aortic aneurysm, and aortic dissection. The 15-year survival has been reported as 96% if arterial complications were not present and 66% if ischemic events had occurred at the time of diagnosis. Complications develop in approximately half of cases and are more likely in smokers.

Treatment

No data are available to guide long-term follow up. As a rule of thumb, clinic visits should be scheduled every 1 to 3 months in the first year after diagnosis and every 3 to 6 months thereafter. Visits should include clinical assessments and ESR and CRP measurements with the proviso that inflammatory markers levels may not reliably indicate TA disease activity, especially late in the disease course when neurologic symptoms occur. A major relapse is defined as new ischemic symptoms or progressive inflammatory changes. Minor worsening includes isolated symptoms consistent with polymyalgia rheumatica (ie, muscle pain and tenderness) and may or may not be associated with increased ESR or CRP levels. Although an increase in inflammatory markers may prompt new vascular imaging, the changes should not, on their own, result in new treatment unless new ischemic symptoms are also present. Regardless of the medical regimen, sequential imaging of the aorta for evidence of disease progression is required.

A systematic review of available therapies found studies are small and often of poor quality; as a result, guidelines for treatment await more robust trials. Clinical trials will be difficult to conduct because of the low prevalence of TA and difficulties in making an early diagnosis. Disease management generally requires a multidisciplinary team including rheumatologists. Differentiating active disease from residual damage is key.

Glucosteroids

Glucosteroids are the mainstay of treatment (Table 2), usually started at 1 mg/kg/day of prednisone or equivalent for 3 to 6 months. Because glucosteroids have a high risk of side effects, progressive reduction of the dose is recommended. Relapses usually prompt an increase in the glucosteroid dose or adding an additional agent (Table 2).

Antirheumatologic Agents

Most people will need a second conventional disease-modifying agent. The guidelines by the European League Against Rheumatism (EULAR) provide recommendations for management of TA. Several conventional antirheumatologic agents have shown efficacy in case series, but the level of evidence is relatively low. These agents may slow angiographic worsening and facilitate lowering of the dose of glucosteroids (Table 2). In general, these agents are considered first-line maintenance therapy for the treatment of children with TA. Intravenous administration of cyclophosphamide is preferred over an oral route because of lower toxicity, better adherence, and comparable efficacy. Several biologic antirheumatologic agents show promise as disease-modifying treatments. Tocilizumab (TCZ) or TNF-α inhibitors should be used when there is high risk of early relapses, the development of new vascular lesions or complications, and the inability to achieve low doses of glucosteroids. The antiTNF-α agents and TCZ may slow angiographic changes and individual cases of remission after treatments with these agents have been reported. In a retrospective review of 46 people with TA in France who were treated with TCZ, reduced doses of glucosteroids and better event-free survival were seen compared with people with TA who had

<table>
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<th>General medical management</th>
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<th>Glucosteroid immunosuppression</th>
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<td></td>
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<td>Traditional antirheumatologic agents</td>
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| • Limit side effects of glucosteroids | • Open surgical repair  
• Endovascular interventions | • Azathioprine  
• Cyclophosphamide  
• Leflunomide  
• Methotrexate  
• Mycophenolate mofetil  
• Rituximab | • Interleukin-6 antagonists  
• Tocilizumab (TCZ)  
• Tumor necrosis factor-α inhibitors |

TABLE 2. TREATMENT OPTIONS FOR TAKAYASU ARTERITIS
other disease-modifying agents. There is some evidence that the TNF-α inhibitors and interleukin-6 antagonists are effective in the treatment of TA.17

Antiplaetlet and Other Antithrombotic Agents

Antiplaetlet agents are helpful for individuals with TA who had ischemia, osteoporosis prophylaxis, gastric protection, antibiotic prophylaxis against pneumocystis pneumonia, sperm cytospertion (postpubertal males), and treatment of hypertension.11 Because of the risk of bleeding complications, the EULAR guidelines do not recommend routine use of antithrombotic agents.7 A small observational study, however, reported fewer ischemic complications among participants taking antiplatelet agents.18 Because of the high risk of recurrent stroke among people who have already had stroke secondary to TA, use of antiplaetlet agents makes sense. There are, however, no data about which antiplatelet agent is preferred or about the usefulness of combinations of antiplaetlet agents. Aspirin monotherapy may be the best option. Because the arterial disease affects multiple arteries, blood pressure management is challenging.

Surgical Intervention

Surgical interventions are often performed during the late stages of TA. Options include both open and endovascular approaches. Both are complex because of the inflammatory nature of the disease and the length and location of the arterial pathology. There are no trials directly comparing open surgery versus endovascular treatment. In general, the indications for revascularization include severe hypertension from renal or aortic stenosis, cerebral or limb ischemia, or an aneurysm of the aorta or another major artery.2,11 Another reason for surgery is the presence of occlusive vascular lesions that persist despite medical treatment. In general, elective operations should be done during a remission to promote improved recovery. Emergency operations are necessary for aneurysm formation, aortic dissection, or critical ischemia including stroke. The choice of surgical procedure depends on the anatomic location and timing of the operation. Emergency surgery during an active disease phase carries a high risk of complications.

In a series of 29 patients seen in a single center over approximately 25 years, all had ischemic neurologic symptoms, 17 had bypass procedures, and 12 had endovascular interventions.19 Surgery was performed during an active-disease phase in 9 individuals, and only 1 had a postoperative stroke. Of the 17 who had bypass operations, 9 developed postoperative hyperperfusion. Long-term patency was excellent with the bypass procedures suggesting the utility of endovascular treatment for short lesions. A single center report of surgical treatment of TA described outcomes in 20 people (15 women with a mean age of 38).20 The operations were done, on average, approximately 6 years after initial diagnosis and were performed on the aorta or its major branches. Stroke occurred in 2 people, and 4 of 32 grafts were occluded at follow up a mean 39 months after the procedure.

Conclusion

Although most neurologists will never see a patient with TA, it does occur with sufficient frequency that the condition should be sought, particularly in a young woman with an atypical stroke. Extending the physical examination to include assessment of the blood vessels in the upper extremities and the abdomen will increase the likelihood of the diagnosis of TA. The associated findings on examination are fairly stereotyped and the assessment, which focuses on vascular imaging of the chest, neck, and head, is relatively straightforward. Management is complex and should be coordinated with rheumatologists with therapies aimed at immune suppression and maintaining perfusion to the brain and other organs.


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Disclosure
HPA reports no disclosures