Challenge of Identifying the Cause of Intracranial Artery Stenosis in Patients With Ischemic Stroke

Sylvain Lanthier, MD, OD, CSPQ; Céline Odier, MD; Sophia Sundararajan, MD, PhD; Daniel Strbian, MD, PhD

Case Description
A 49-year-old white, right-handed, nonmigraineur woman sought medical attention at a secondary-level hospital because of an unusual headache that has lasted 3 days. She was a cigarette smoker and had a history of depression, for which she was treated with trazodone. She had a previous episode 2 years before presentation of transient right facial palsy, and brain MRI at the time showed multifocal chronic infarcts in the middle cerebral artery (MCA) territory bilaterally, and an acute watershed infarct on the left MCA (Figure 1). Blood tests and cerebrospinal fluid analysis had been unremarkable. She was then lost to follow-up.

During the current admission, she reported asthenia and lack of attention for the previous 6 months. After lifting heavy boxes, she developed a mild occipital headache that gradually worsened >3 days to become severe and pulsatile. Other than an asymmetrical blood pressure, which was lower on the right arm than on the left, her vital signs were normal. Her neurological examination revealed memory impairment, ideational apraxia, visual agnosia, left homonymous hemianopia, facial asymmetry, sensory ataxia, and sensory extinction. Systemic examination was unremarkable. Brain MRI (Figure 2) showed the chronic changes that were seen on her previous MRI, 2 years earlier and a new acute right posterior cerebral artery infarct with mass effect, and no crescent sign on T1-weighted imaging with fat saturation. Computed tomographic angiography and catheter angiography documented occlusion of the right posterior cerebral artery, severe stenosis of the left, and occlusion of the right distal M1 segments of the MCAs with prominent lenticulostriate and pial perforating arterioles. In addition, there was 70% stenosis of the right subclavian artery and minimal plaques at the carotid bifurcation bilaterally. ECG revealed QS complexes in V1 through V3 leads. Echocardiography documented a left ventricle apical aneurysm without intracardiac thrombus. Cardiac telemetry was normal. Blood test results were normal, including complete blood count, glucose, HbA1c, low-density lipoprotein, homocysteine, creatinine, electrolytes, troponins, coagulation tests (activated partial thromboplastin time, international normalized ratio, lupus anticoagulant, anticardiolipins, and anti–β(2)-glycoprotein type 1 antibodies), erythrocyte sedimentation rate, C-reactive protein, fibrinogen, autoantibodies (antinuclear, anti-DNA, extractable nuclear antigen, antineutrophil cytoplasmic, and rheumatoid factor), complement C3 and C4, and infection screening (hepatitis B surface antigen, anti-hepatitis C virus antibody, venereal disease research laboratory, and anti-HIV). Cerebrospinal fluid was collected from lumbar puncture 11 days after the onset of headache revealing lymphocytic pleocytosis (14×10³ cells/L), increased proteins (0.61 g/L), normal glucose, and negative stains, cultures, polymerase chain reaction for herpes viruses and venereal disease research laboratory. A diagnosis of central nervous system (CNS) vasculitis was considered. The patient underwent open brain and leptomeningeal biopsy, which showed normal tissue, including intact small-vessel structure. Coronary angiography revealed multifocal atherosclerotic changes, including occlusion of the left anterior descending artery. Bare metal stents were deployed in the right coronary artery, the circumflex artery, and its M2 branch. She was discharged on warfarin plus clopidogrel for 1 month, and aspirin, atorvastatin, metoprolol, and ramipril.

The patient was then transferred to our tertiary center for outpatient clinical follow-up. Her headaches resolved over several weeks. She still had asthenia, mild memory problems, and a left homonymous hemianopia. She was found to have insulin resistance. Although she initially quit smoking after the stroke, she resumed several months later. Four and half years later she had no new symptoms.

Discussion
This case illustrates some of the challenges of understanding the cause of intracranial artery stenosis in patients with ischemic stroke. We felt that intracranial atherosclerosis was the most likely explanation for her stenosis and tailored secondary prevention at our tertiary center accordingly with antiplatelet, antihypertensive, and statin drugs. Our patient’s relatively
young age, absence of obvious risk factors other than cigarette smoking (she had insulin resistance, but we did not know that initially), and the absence of significant stenosis in the carotid and vertebral arteries were initially misleading. In a large Finnish series using the Trial of Org 10172 in Acute Stroke Treatment classification, large-artery atherosclerosis was responsible for only 4% of ischemic strokes occurring between aged 15 and 44 years, but this proportion increased to 12% in the age group 45 to 49 years. Extracranial cervical artery atherosclerosis is primarily seen in whites with ischemic stroke. In young Asians, as many as 41% of ischemic strokes would be characterized as large-artery atherosclerosis, with predominant intracranial involvement by Trial of Org 10172 in Acute Stroke Treatment criteria. Because advanced imaging techniques are more commonly used, intracranial stenosis may be detected more often and the use of less stringent diagnostic criteria may further add to a perceived increase in the prevalence of intracranial stenosis. In our patient, the diagnosis of intracranial atherosclerosis is supported by our identification of an additional risk factor, insulin resistance, and the involvement of other arterial beds, including the subclavian and coronary arteries.

A diagnosis of CNS vasculitis was considered. Primary angiitis of the CNS (PACNS) is a rare and life-threatening form of vasculitis confined to the CNS. Neurological manifestations of PACNS include headaches, focal deficits, cognitive decline, and seizures. Unless treated with potent immunosuppressant agents, PACNS often follows a progressive and relapsing course, leading to severe morbidity or death. A timely and accurate diagnosis is, therefore, important. Unfortunately, neither the neurological manifestations nor the results of noninvasive investigations are specific to PACNS, and the differential diagnosis is vast, including many conditions that are considerably more common. Brain and leptomeningeal biopsy may confirm the vasculitic process, but this procedure is invasive, possibly morbid and associated with a 25% to 50% risk of false-negative results, especially when the disease is limited to the larger intracranial arteries. The usual diagnostic approach consists of excluding potential mimicking conditions through a complete investigation, and to reserving CNS biopsy for selected patients whose symptoms remain otherwise unexplained. Potential mimickers of PACNS include systemic vasculitis and vasculitis secondary to cancer, infection, connective tissue disease, and other conditions. In our patient, these are considered unlikely because of normal erythrocyte sedimentation rate and C-reactive protein levels, angiographic changes consistent with coronary and subclavian atherosclerosis. Headaches, CNS lesions on MRI, and cerebrospinal fluid inflammation are all highly prevalent in PACNS, and the absence of any one of these findings should make the physician question the diagnosis of PACNS. In our patient, several elements argue against a diagnosis of PACNS. The interval of 2 years between 2 ischemic events would be inconsistent with PACNS. In contrast to the subacute or chronic headaches of PACNS, our patient’s headache was recent and probably because of the acute brain infarct with mass effect, rather than a prodrome. Although the patient had mild cerebrospinal fluid changes, these likely were secondary to her infarct and did not necessarily imply vasculitis. Finally, vascular changes of PACNS tend to predominate in small-sized arteries, frequently beyond the resolution of vascular imaging. These differ from the striking medium-sized intracranial artery findings seen in our patient. High-resolution vessel wall MRI may help differentiate the causes of medium intracranial artery stenosis (Table).

Symptom onset after Valsalva maneuver in the presence of a left ventricle apical aneurysm and the posterior cerebral artery location raises the possibility of a cardioembolic cause. However, this mechanism would not explain severe stenosis or occlusion of both MCA with corresponding symptoms limited.
to a transient facial asymmetry that occurred two years before her PCA stroke. Furthermore, we considered the watershed pattern of chronic cerebral infarcts and the compensatory dilation of perforating arterioles as reflecting chronic bilateral MCA stenosis.

In conclusion, identifying the cause of intracranial artery stenosis can be challenging in patients with stroke, but it is critical for secondary prevention. The treatment includes antithrombotic therapy, control of relevant vascular risk factors, and specific therapies (eg, immunosuppressant drugs in PACNS and anticoagulant treatment in cardioembolic stroke).

**TAKE-HOME POINTS**

- Determining the cause of intracranial artery stenosis is important for optimal secondary prevention.
- A diagnosis of intracranial atherosclerosis is more likely in patients aged >45 years who have vascular risk factors and evidence of vascular disease in extracranial locations.
- Because persistent headaches, cerebrospinal fluid inflammation, and changes on brain MRI are frequent in Primary angiitis of the central nervous system, this diagnosis is unlikely and it may be appropriate to defer central nervous system biopsy in patients with only one of these manifestations.

**Key Words:** intracranial atherosclerosis  primary angiitis of the central nervous system  stroke

**References**


**Disclosures**

None.
Challenge of Identifying the Cause of Intracranial Artery Stenosis in Patients With Ischemic Stroke

Sylvain Lanthier, Céline Odier, Sophia Sundararajan and Daniel Strbian

*Stroke*. 2015;46:e59-e61; originally published online December 18, 2014;
doi: 10.1161/STROKEAHA.114.007419

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/46/3/e59

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/