A 27-Year-Old Man With Right-Sided Hemiparesis and Dysarthria

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The Neurohospitalist
2016, Vol. 6(4) 174-180
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DOI: 10.1177/1941874416648197
nhos.sagepub.com

A 27-year-old African American male with no significant past medical history presented to a local hospital after acute-onset right hemiparesis and difficulty speaking. At that time, magnetic resonance imaging (MRI) revealed an acute infarct in the left posterior thalamus and left posterior internal capsule. Magnetic resonance angiography (MRA) revealed proximal basilar occlusion and absence of the left posterior communicating artery (PComm). The patient was taken to angiography, which revealed occlusion of the proximal third of the basilar artery with the distal portion supplied by the right PComm. According to the report, the lumen was irregular, suggestive of stenosis rather than thrombus. Given an improved and stable neurological examination, therapeutic intervention was deferred. His workup revealed no history of smoking, normal blood pressure, no history of hypertension, an LDL of 75, and hemoglobin A1C of 6.4, despite normal fasting glucose. In addition, he was found to have positive anticardiolipin antibodies, and given his relative lack of vascular risk factors, it was thought a hypercoagulable state was the most likely cause of his stroke. He was started on warfarin for anticoagulation.

However, within a few days, during this initial hospital stay, he developed a fluctuating course with a pressure-dependent neurological examination, with worsening hemiparesis and confusion when systolic pressures dropped below 125 mm Hg. He was transferred to our tertiary care institution where he was noted to have mild right hemiparesis and mild dysarthria consistent with his known left thalamic and capsular infarct. Further imaging was done on admission including computed tomography (CT) angiography of the head and neck, which revealed high-grade stenosis of the mid-basilar artery measuring 5 mm in length (Figure 1). He was treated with vasopressors to maintain his blood pressure while awaiting normalization of his international normalized ratio.

During that time, an MRI of the brain with and without contrast and an MRA were performed revealing a stable, previously described infarct (Figure 2) and basilar artery occlusion (Figure 3A). However, new findings were also shown including a flow gap and severe narrowing of the right internal carotid artery (ICA) terminus and origins of the left middle cerebral artery (MCA) and left anterior cerebral artery (ACA;

Figure 3B). In addition, postcontrast images revealed vessel wall enhancement of the bilateral vertebral arteries, suggestive of vasculitis.

Differential Diagnosis

Discussant: Amer Malik

Stroke is a common encounter for the neurohospitalist. However, ischemic stroke in the young is more unique and requires a broader differential. Although many strokes in young adults are also attributable to cardioembolism and atherosclerosis, one must also consider nonatherosclerotic vasculopathies, coagulopathies, hematologic diseases, inflammatory diseases, and infection.¹

Cardioembolic sources have been shown to cause anywhere from 10% to 34% of strokes in young adults in various case series.²⁻¹⁰ Given the relative low probability in young adults of known major risk sources of embolism, one must also consider the low-risk sources, including patent foramen ovale, recent atrial septal aneurysm, spontaneous echo contrast that is indicative of atrial stasis, cardiac valvular disease, and ventricular akinesis without heart failure.

Atherosclerotic strokes in young adults are generally more rare, with multiple case series finding large artery atherosclerosis comprising between 4% and 20% of strokes and small-vessel disease comprising between 3% and 26% of strokes, respectively.²⁻¹⁰ Studies have found associations between atherosclerotic etiology and known vascular risk factors in young adult patients with stroke including hypertension, hyperlipidemia, and smoking.^{3-6,11} As a result, conventional stroke workup should be completed in all

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Figure 1. Computed tomography (CT) angiography reconstruction of the head and neck showing patent carotid arteries and anterior circulation (A) and occluded versus high-grade stenosis of basilar artery (arrow, B).

Figure 2. Magnetic resonance imaging (MRI) of the brain showing subacute infarction with restricted diffusion still present on diffusion-weighted imaging (DWI) (A), mild hypodensity and isointensity on indicates apparent diffusion coefficient (ADC) (B), and signal changes already present on FLAIR (C). FLAIR indicates fluid-attenuated inversion recovery.

patients with stroke, and vascular risk factors should be managed as with stroke in older patients.

Nonatherosclerotic vasculopathies associated with stroke include moyamoya disease, cerebral amyloid angiopathy, fibromuscular dysplasia, reversible cerebral vasoconstriction syndrome, Sneddon syndrome, dilatative dolichoectasia, arterial trauma, and, most commonly, arterial dissection.^{12,13} Cerebral arterial dissection can account for up to 25% of stroke in young adults and may result from either major or minor trauma, such as manipulations and valsalva.^{9,14,15} They may present with both local and ischemic manifestations, the latter of which occurs more often when luminal narrowing is present.¹⁶ With carotid artery dissections, one may expect local symptoms of Horner syndrome, neck pain, headache, tinnitus, facial pain, and cranial nerve palsies. Ischemic sequelae include stroke, commonly in the MCA territory, and ophthalmic manifestations including amaurosis fugax, ischemic optic neuropathy, and retinal infarction. Vertebral dissection may cause local symptoms of posterior headache

or neck pain, cervical root involvement, and lower brain stem compression from intracranial dissection. Ischemic signs include stroke in posterior circulation, subarachnoid hemorrhage, and spinal cord infarct. Noninvasive imaging with either MRA or CT angiography is the mainstay of diagnosis. Coagulopathy and hematologic diseases are both uncommon causes of stroke in young adults. Hematologic diseases leading to stroke usually include sickle cell disease and myeloproliferative disorders, which can cause arterial occlusion. Coagulopathies causing stroke in young adults may be either inherited or acquired and are thought to cause paradoxical emboli leading to stroke. The inherited coagulopathies most often associated with thromboembolic disease include factor V Leiden and activated protein C resistance, prothrombin gene mutation, protein S deficiency, protein C deficiency, and antithrombin III deficiency.¹⁴ Acquired coagulopathies include active oral contraceptive use and/or hormone replacement therapy, smoking, pregnancy, cancer, and antiphospholipid antibody syndrome (APLAS). Testing for these

Figure 3. A, Magnetic resonance angiography (MRA) showing persistent basilar occlusion versus high-grade stenosis (arrow). B, Magnetic resonance angiography reconstruction showing new flow gap and severe narrowing of right ICA terminus (arrow) and origins of the right MCA and right ACA (arrowheads). C, Magnetic resonance angiography reconstruction showing resolved flow gap and narrowing of right ICA terminus and origins of the right MCA and right ACA (arrow). D, Magnetic resonance angiography showing persistent basilar occlusion versus high-grade stenosis (arrow). ACA indicates anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery.

hypercoagulable states should be tailored to high-risk populations with younger age, cryptogenic stroke, thrombotic events, multiple miscarriages, and family history of thromboembolic disease. Because antibodies associated with APLAS can be transiently elevated, the diagnosis requires demonstration of positive antibodies on 2 occasions more than 12 weeks apart. This patient should not have been diagnosed with APLAS and started on anticoagulation on the basis of a single positive anticardiolipin antibody. Inflammatory causes of stroke in the young include primary vasculitides. Primary central nervous system (CNS) vasculitis is a giant cell arteritis limited to the brain and spinal cord that occurs more frequently in men, with median age of 50, although it may present at any age.¹⁷ It most often presents with headache and altered mental status but may also manifest with strokes, cranial nerve palsies, and myelopathies.^{17,18} Diagnosis can be suspected with angiographic findings of arterial beading but can only be confirmed by brain and leptomeningeal biopsy. Treatment consists of

immune-modifying therapies including corticosteroids and cyclophosphamide.¹⁹ Temporal arteritis can cause stroke in addition to ischemic optic neuropathy, but it almost never occurs in patients younger than 50 years.²⁰ Takayasu arteritis affects large vessels, typically the aorta and its branches, and can cause stroke from carotid and vertebral artery involvement.²¹ It most often presents in women aged 10 to 40 years and should be strongly considered in patients with diminished peripheral pulses and vascular bruits; diagnosis is made by CT or MR angiography of the great vessels.^{22,23} Systemic vasculitides that can cause ischemic stroke include Behcet disease, polyarteritis nodosa, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. Clues to these diagnoses include involvement of other organ systems such as the kidneys, skin, lungs, gastrointestinal tract, and sinuses. With the exception of Behcet disease, neurological involvement is more often peripheral with mononeuritis multiplex, and isolated strokes in these conditions are rare.

Systemic lupus erythematosus (SLE) can cause cerebral infarction through cardioembolism with Libman-Sacks endocarditis, hypercoagulable state with SLE-associated APLAS, or occlusion of intracranial arterioles and capillaries via immune-complex deposition and activation.²⁴ Sjogren syndrome is rarely associated with CNS vasculitis and stroke.²⁵ In both of these systemic diseases, there should be prominent non-CNS signs and symptoms as well.

Infectious vasculitis may also present with stroke syndromes. Etiologies include viral, bacterial, and parasitic. Varicella zoster virus (VZV) infects more than 95% of the world's population. Rarely during reactivation, especially in immunocompromised patients, the virus may invade the cerebral arteries and produce a VZV vasculopathy leading to ischemic stroke.²⁶ Cerebrovascular disease in the setting of HIV provides a challenging diagnostic spectrum as the entity of HIV vasculopathy exists, but opportunistic infections may account for the majority of pathology and should be thoroughly investigated.²⁷ *Treponema pallidum*, the infectious bacterium of syphilis, may invade subarachnoid vessels leading to meningovascular neurosyphilis and subsequent infarctions.^{28,29} Although they cause more of a meningitis-like picture, *Borrelia burgdorferi*, *Bartonella*, and *Mycobacterium tuberculosis* may also cause a vasculitic picture and stroke.³⁰⁻³² In addition, subarachnoid cysticercosis has been shown to involve medium-sized cerebral vessels causing stroke.³³ Diagnostic studies for these etiologies should include lumbar puncture and cerebrospinal fluid (CSF) examination for chemistry, cell count, cultures, specific antibodies, and polymerase chain reaction (PCR).

Our patient's presentation of right hemiparesis and dysarthria is consistent with his left thalamic and capsular infarct in the territory of the tuberothalamic branch of the posterior communicating artery. Atherosclerosis is an unlikely cause, as he does not have significant vascular risk factors, and he developed new stenosis at a rapid rate. In addition cardioembolic sources are unlikely, as the etiology appears to be a vasculopathy. Given that his imaging is not consistent with a dissection, we must consider other causes of vasculopathy. The findings of new, rapidly developing stenosis, along with gadolinium enhancement of vessel walls, are more concerning for a vasculitic process rather than the initial diagnosis of able state.

Vasculitides as described earlier include a broad group of diseases. Within the primary vasculitides, primary CNS vasculitis was the most likely etiology, as it involves only CNS vasculature as was the case with our patient. Temporal arteritis was unlikely, given that this disease almost never occurs in patients younger than 50 years. Takayasu arteritis was also unlikely, as the patient had no aortic arch or proximal branch involvement. Behçet disease was less likely, as there was a lack of oral or genital ulcers. Polyarteritis nodosa was also not likely, as the patient did not exhibit any multisystem symptomatology. Additionally, strokes associated with this disease are mostly lacunar in nature. Finally, Wegener and Churg-

Strauss were unlikely, given the lack of lung, airway, ear, or skin manifestations. Regarding secondary vasculitides, those associated with Sjogren should have an associated sicca syndrome. Systemic lupus erythematosus is not as easily ruled out, as it is such a heterogeneous illness; however, no typical signs of malar rash or renal dysfunction were noted. The infectious vasculitides remain a possibility, including those secondary to VZV, HIV, meningovascular neurosyphilis, and tuberculosis. Cysticercosis is less likely, as the patient did not have any travel to an endemic area, and Lyme is also unlikely, as he did not travel outside the state of Florida. *Bartonella* should be discounted, as the patient had no contact with cats or history of lymphadenopathy.

Although clinically the differential is somewhat broad, diagnosis of many of the remaining possibilities is straightforward with a number of readily available serological tests on blood and spinal fluid.

Diagnosis and Treatment

During the course of his hospital stay, it was noted that the patient had disseminated anal warts. On further questioning, the patient admitted to a previously undisclosed diagnosis of HIV that was reaffirmed with a positive HIV 1/2 antibody and an absolute CD4 count of 15. He had not taken antiretroviral treatment at any time since this diagnosis 8 years prior.

Infectious causes of vasculitis in the setting of untreated HIV were then primarily considered, including meningovascular neurosyphilis, VZV, HIV-related disease, and *M. tuberculosis*. Neurosyphilis may present at any stage of infection and encompasses ocular neurosyphilis, parenchymal neurosyphilis such as Tabes dorsalis and general paresis as well as meningovascular syphilis.³⁴ Meningovascular neurosyphilis is a secondary syphilis that occurs when the pathogen invades the meninges, usually within the first 10 years of infection, but may occur within months in an HIV-infected patient.^{35,36} This process may be followed by a meningitis-like picture with fever, confusion, and neck stiffness, or the patient may remain asymptomatic.³⁷ The disease can then spread to the vasculature, causing vasculitis presenting as either acute or subacute stroke symptoms.³⁷ Angiographic findings are nonspecific, but when compared to common atherosclerotic disease, there is more likely to be involvement of the supraclinoid ICA, and plaques are more likely to be smoother and longer.³⁸ Varicella zoster virus vasculopathy occurs weeks to months after a zoster reactivation, although this may occur in the absence of the classic rash.³⁹ Angiographic evidence of vasculitis may be absent, as the disease affects large or small vessels, and one must rely on imaging findings of ischemic lesions and CSF studies positive for VZV PCR or immunoglobulin G (IgG).⁴⁰ The VZV PCR may not always be reliable, as the vasculopathy can develop some time after infection. Cerebrospinal fluid anti-VZV IgG is more convincing of CNS varicella, and perhaps most convincing is demonstration of intrathecal anti-VZV IgG synthesis demonstrated by a lower ratio of serum-

CSF anti-VZV IgG when compared to serum–CSF ratio of albumin or IgG.³⁹ HIV-related vasculopathy might be a diagnosis of exclusion, given the high burden of opportunistic diseases that may be involved. Tuberculous meningitis has long been associated with stroke as visualized on both pathological and imaging studies.^{41,42} Angiographically, the arteries most affected are the supraclinoid ICA, MCA, and ACA. Strokes often occur in a “Tuberculous (TB) zone” of the medial lenticulostriate and thalamoperforating vessels.⁴³ Diagnosis can be made on the basis of CSF studies, which should show increased protein, low glucose, and mononuclear pleocytosis, usually between 100 and 500 cells/ μ L.⁴⁴ Acid-fast bacilli stain should be sent and may be repeated if initially negative, as the sensitivity of this test increases with repeated sampling.⁴⁵

Lumbar puncture revealed no red blood cells, 30 white blood cells (95% lymphocytes), glucose 38, and protein 54. Gram stain showed moderate white blood cells and no organisms. India ink and acid-fast bacilli stain were both negative. Serum rapid plasma reagin (RPR) was reactive with a titer of 1:2048, and CSF-VDRL was also reactive. The patient was diagnosed with meningovascular neurosyphilis and started on penicillin G. Additional CSF studies showed negative bacterial, fungal, and viral cultures; negative cryptococcal antigen (negative serum antigen as well); and negative PCR for varicella zoster, cytomegalovirus, herpes simplex virus (HSV) 1, and HSV 2. These data further discounted alternative infectious diagnoses.

The patient was treated for 14 days with intravenous (IV) penicillin G at a dose of 4 million units every 4 hours, with plans for another dose of 2.4 million units intramuscularly 1 week after completing the IV regimen for treatment of neurosyphilis. Over the course of his treatment, the patient’s symptoms improved with resolution of the right hemiparesis and only mild dysarthria noted on discharge. Repeat imaging done prior to his discharge showed resolution of flow gap and severe narrowing of right ICA terminus and origins of right MCA and right ACA but persistent basilar artery occlusion versus severe stenosis (Figure 3C and D).

Discussion

This case demonstrates meningovascular syphilis presenting as stroke in a patient with no known previous diagnosis of syphilis. Syphilis infection can be divided into 3 stages: “primary” during the initial infection, “secondary” during hematogenous spread of the pathogen, and “tertiary” occurring months to years after initial infection. Tertiary syphilis is most often used in describing gummas, cardiovascular syphilis, luetic osteitis, and parenchymal neurosyphilis.³⁴

However, neurosyphilis may describe any involvement of the CNS at any stage of infection.³⁴ Invasion of the CNS usually occurs within the first few months to years of infection but may remain dormant for years afterward.³⁵ Inflammatory manifestations, including meningeal and meningovascular

neurosyphilis, usually occur within the first few years of infection, whereas more parenchymal diseases, such as tabes dorsalis and general paresis, usually occur much later. Ocular neurosyphilis may occur early or late.⁴⁶

Diagnosis is generally made from the clinical presentation and presence of CSF abnormalities, including pleocytosis and elevated protein, or the gold standard of CSF-VDRL. However, CSF-VDRL can have a broad range of sensitivity as widespread as 30% to 70%.^{47–49} This reported variability causes some difficulty in diagnosing neurosyphilis in patients with HIV, as HIV itself may cause CSF pleocytosis,⁵⁰ and a negative CSF-VDRL does not exclude the disease. Some studies have found predictors of neurosyphilis in patients with HIV including RPR titers $\geq 1:32$ and CD4 counts $\leq 350/\mu$ L.^{51–53} In addition, some clinicians use CSF WBC count of $>20/\mu$ L as the threshold for treatment of neurosyphilis in patients with HIV, while a CSF WBC count of ≤ 5 is not likely to be found in neurosyphilis. When CSF shows only a mild pleocytosis of CSF WBC 6 to 20, CSF fluorescent treponemal antibody absorption (FTA-ABS) can direct toward treatment if positive and more definitively exclude neurosyphilis if non-reactive.⁵¹ As CSF FTA-ABS is sensitive but not specific, if this test returns negative one may exclude a diagnosis of neurosyphilis with more confidence.⁵⁴ In the setting of clinical suspicion for neurosyphilis in patients with HIV, it may be prudent to initiate treatment, despite negative CSF-VDRL if patients have RPR titers $\geq 1:32$, a CSF pleocytosis between 20 cells/ μ L and 350 cells/ μ L, and positive CSF FTA-ABS.

Regarding neurosyphilis treatment, the Center for Disease Control (CDC) recommends high-dose IV penicillin G 24 million units daily (as either continuous infusion or divided into 6 doses) for 10 to 14 days.⁵⁵ Success is often gauged clinically by resolution or stabilization of neurological symptoms and by CSF normalization. The CDC recommends testing CSF every 3 to 6 months after treatment. If pleocytosis does not improve by 6 months or CSF-VDRL does not decline 4-fold or to nonreactive status after 1 year or CSF abnormalities persist for 2 years, the patient should likely be treated again.⁵⁵

Conclusion

In cases of ischemic stroke in young patients, evaluation should begin by ruling out the most likely etiologies of cardioembolism, nonatherosclerotic vasculopathies, especially arterial dissection, and atherosclerosis, which are evaluated in most standard stroke workups that include echocardiograms, intracranial and extracranial vessel imaging, and laboratory evaluations of vascular risk factors. Once these etiologies are excluded, it is also important to evaluate the less common causes of stroke including coagulopathies, hematologic diseases, inflammatory diseases, and infection. Coagulopathies and hematologic diseases should be evaluated first with laboratory panels before evaluating for the more rare causes of inflammatory diseases and infections. At this point,

it is essential to perform a lumbar puncture to look for signs of vasculitis and infection. If the patient shows any other systemic abnormalities, they may direct the physician toward one or more of the inflammatory or infectious etiologies. Patients with HIV should be given extra consideration for infectious etiologies, given their burden of opportunistic infections and the difficulty in diagnosing neurosyphilis in these patients. Prompt treatment may halt the progression and even reverse symptoms and signs of stroke secondary to neurosyphilis as was the case with our patient.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Keywords

central nervous system bacterial infections, central nervous system infections, intracranial arterial diseases, cerebrovascular disorders, stroke, imaging, techniques

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