Stroke in a 36-year-old man with neurosyphilis and HIV, diagnosed using high-resolution vessel wall imaging

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A 36-year-old man presented to the emergency department with sudden-onset dysarthria, right hemifacial droop, right hemiparesis and right dysmetria, which had started the day before. He was an active smoker (5 pack-years), drank an average of 3 alcoholic beverages per week and said that he had used cocaine, methamphetamines and cannabis but no intravenous drugs. He reported being sexually active with men and women and used condoms inconsistently. He had no headaches or systemic symptoms. When we examined him, he appeared cachectic but in no acute distress. His systolic blood pressure was 150 mm Hg, and other vital signs were normal. He was alert and oriented, and language examination — including naming, fluency and comprehension — was normal. He had mild dysarthria, right hemifacial weakness sparing the upper face, and right proportional hemiparesis, Medical Research Council grade 4/5. There was right-sided hyperreflexia and an upgoing right plantar response, corresponding to an upper motor neuron weakness pattern. The finger-to-nose and heel-to-shin tests revealed right-sided dysmetria, and the patient's gait was unstable. Because of the ataxic hemiparesis, we suspected a lacunar infarction, likely in the pons or internal capsule. We performed an urgent computed tomography (CT) scan without contrast of the patient's head, but saw no apparent ischemic or hemorrhagic changes (Figure 1A). Computed tomography angiography of the head showed severe stenosis of his

Key points

- The differential diagnosis of stroke in a young adult includes hereditary and acquired thrombophilias, structural cardiac defects, inflammatory and noninflammatory vasculopathies, infections, and other prothrombotic states, such as malignancy or pregnancy.
- Meningovascular syphilis is one of many forms of neurosyphilis; it affects arteries of all sizes and commonly leads to ischemic stroke in the anterior and posterior circulations.
- Concentric vessel wall enhancement seen on high-resolution vessel wall imaging can help to distinguish inflammatory or infectious vasculopathy from atherosclerotic disease.
- Whenever feasible, histopathologic evaluation should be carried out and correlated with vessel wall imaging findings.

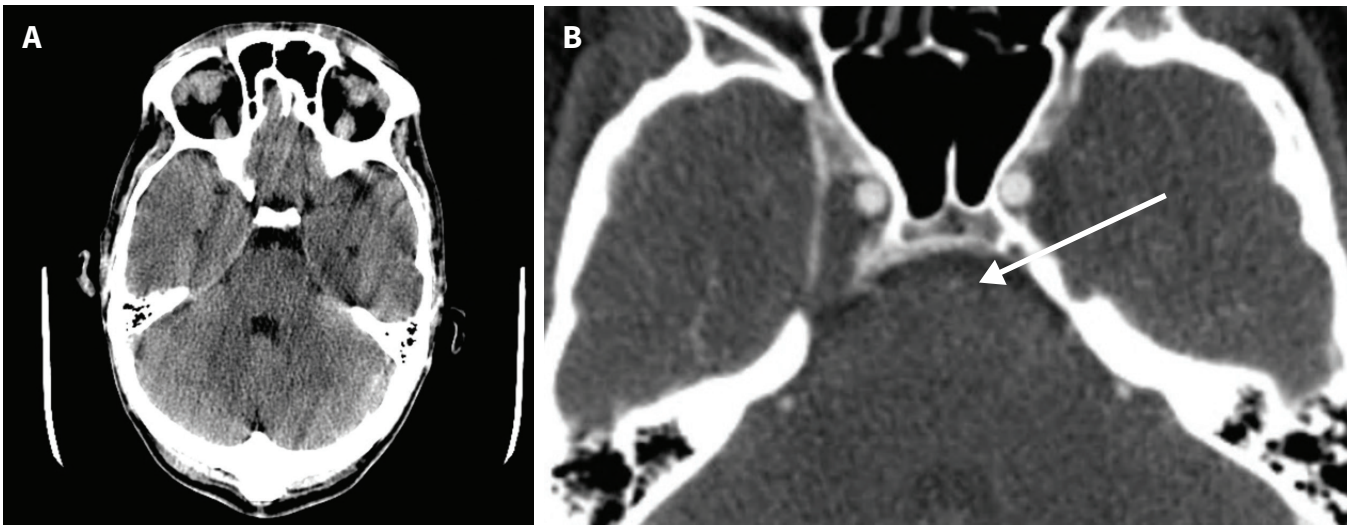

Figure 1: (A) Initial computed tomography (CT) scan of the head of a 36-year-old man, without contrast, showing no evidence of acute bleeding or apparent ischemic changes. (B) Initial head CT angiography showing severe stenosis of the basilar artery (arrow).

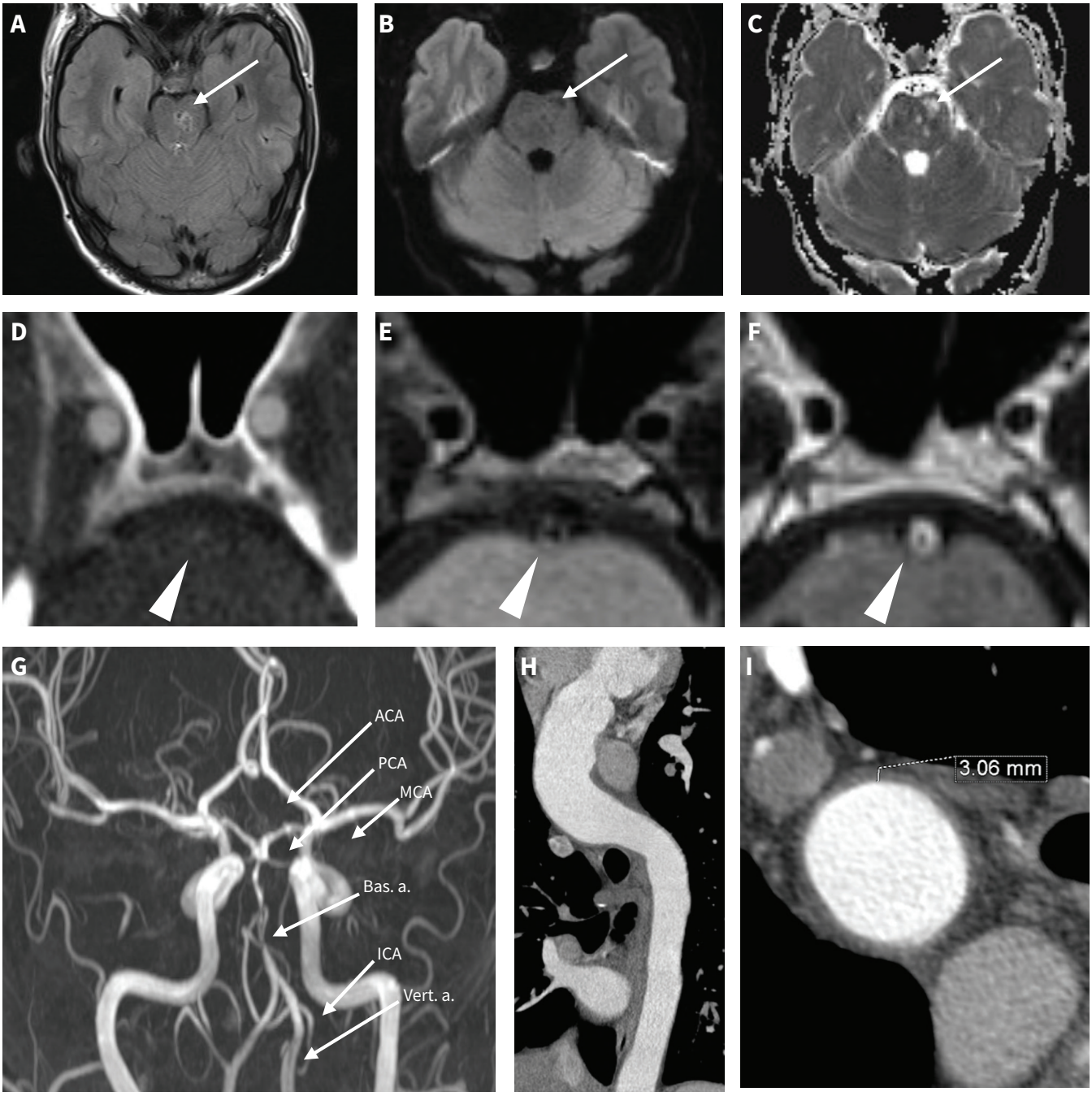

Figure 2: (A–C) Initial MRI scan of the patient's head, showing (arrows) areas of hyperintensity within the left side of the pons on FLAIR (A) and corresponding areas of hypointensity on diffusion-weighted imaging (B) and hyperintensity on the apparent diffusion coefficient map (C) consistent with chronic infarction (> 3 wk old). (D–F) Vessel wall MRI of the basilar artery using 3D T_1 SPACE before gadolinium (E) and after gadolinium injection (F) showing smooth, concentric enhancement of the basilar vessel wall (arrowheads). Sequence parameters: echo time 12 ms, repetition time 700 ms, voxel size 0.8 × 0.8 × 0.9 mm. Material: Siemens 3 T MAGNETOM Skyra MRI scanner, 20-channel head and neck coil. (D) Corresponding CT angiography showing severe stenosis of the basilar artery without evidence of vessel wall plaque or calcification. (G) Coronal MRI maximum intensity projection reconstruction of the intracranial arteries using time-of-flight technique showing multifocal stenosis of the basilar artery and proximal stenosis of the bilateral posterior cerebral arteries. (H–I) Computed tomography angiography of the thorax with reconstruction along the longitudinal axis of the aorta, showing increased diameter of the ascending aorta, measuring 43.1 mm × 38.4 mm (H), and increased thickness of the aortic wall (I) consistent with aortitis. Note: ACA = anterior cerebral artery, Bas. a. = basilar artery, CT = computed tomography, FLAIR = fluid-attenuated inversion recovery, ICA = internal carotid artery, MCA = middle cerebral artery, MRI = magnetic resonance imaging, PCA = posterior cerebral arteries, SPACE = Sampling Perfection with Application-optimized Contrast using different flip angle Evolution, Vert. a. = vertebral artery.

basilar artery (Figure 1B), as well as irregularities in the proximal portion of the posterior cerebral arteries, the middle cerebral arteries, and the right anterior cerebral artery. Computed tomography angiography of the cervical arteries showed no atheromatous plaque or stenosis.

The multiple areas of proximal cerebral artery stenosis on the patient's CT angiography made us consider a nonatherosclerotic vasculopathy in the differential, given his age and lack of cardiovascular disease history. Nonatherosclerotic vasculopathies encompass many entities, such as arterial dissection, fibromuscular dysplasia, collagenopathies, primary central nervous system (CNS) vasculitis, systemic vasculitides, infectious vasculopathies, moyamoya syndrome and disease, radiation-induced vasculopathy, drug-related vasculopathy and reversible cerebral vasoconstriction syndrome (RCVS).[1] In addition to intracranial atherosclerosis, pertinent diagnostic considerations in our patient included systemic or primary CNS vasculitis, infectious vasculopathy and drug-related vasculopathy.

Serum laboratory investigations showed reactive syphilis enzyme immunoassay (EIA), reactive rapid plasma reagin and reactive HIV EIA. The patient's CD4 count was 0.23 × 10^9/L. His serum cholesterol level was 4.78 (normal 4.20–5.20) mmol/L, high-density lipoprotein level was 0.90 (normal 0.90–1.80) mmol/L, low-density lipoprotein level was 3.33 (normal 2.20–3.40) mmol/L, glycosylated hemoglobin level was 65%, C-reactive protein was < 4 (normal 0–10) mg/L, antinuclear antibody was weakly reactive (1/40), international normalized ratio was 0.92, partial thromboplastin time was 23 (normal 22–29) seconds, platelets were 249 (normal 130–400) × 10^9/L, and anticardiolipin and anti-β2 glycoprotein testing was negative. Cerebrospinal fluid analysis showed a leukocyte concentration of 130 (normal < 5) cells/μL, protein 0.88 (normal 0.15–0.4) g/L, glucose 2.0 (normal 2.8–4.2) mmol/L, and a reactive venereal disease research laboratory test (1/8). We diagnosed pontine ischemic stroke secondary to meningovascular syphilis in the context of HIV co-infection. An alternative possibility, HIV-associated vasculopathy, could not be completely ruled out in the absence of histopathologic assessment. The patient had never received a diagnosis of syphilis in the past and had never had a positive HIV test.

We treated the patient with acetylsalicylic acid 80 mg/d, rosuvastatin 5 mg/d, and intravenous penicillin G 24 million units/d for 14 days followed by a single dose of intramuscular penicillin G of 2.4 million units. We also started him on active antiretroviral therapy after treating the syphilis.

A magnetic resonance imaging (MRI) scan of the brain a month later showed several foci of infarction within the pons, including the left paramedian region (Figure 2A). Diffusion-weight imaging and apparent diffusion coefficient sequences did not show any acute infarction, likely owing to the delay in obtaining the MRI (Figures 2B and 2C). We performed contrast-enhanced vessel wall (VW) MRI, which showed circumferential enhancement of the basilar artery, compatible with syphilitic arteritis (Figures 2E and 2F). Additionally, CT angiography of the thorax showed signs of aortitis (Figures 2H and 2I). The patient also underwent a transthoracic cardiac echocardiogram and continuous heart monitor for 48 hours; both were unremarkable.

At a follow-up visit 3 months later, the patient had fully recovered from the ataxic hemiparesis and complained only of mild residual dysarthria. He was lost to follow-up for further imaging.

Discussion

Ischemic strokes in adults younger than 50 years are on the rise worldwide.[2] Important modifiable risk factors include smoking, hypertension, sedentary lifestyle, dyslipidemia, obesity, diabetes mellitus and atrial fibrillation. Large vessel atherosclerosis, cardio-embolic sources and small vessel disease are considerably less common causes of stroke than in older adults. Several rare conditions have been associated with ischemic stroke in younger adults (Box 1).[3] Although uncommon when considered individually, together they could account for 22% of cases in this population.[4]

Syphilis is a recognized cause of ischemic stroke. Soon after inoculation, *Treponema pallidum* disseminates to the cerebrospinal fluid, where it remains dormant in most patients. Without adequate antibiotic therapy, the spirochete can eventually invade the CNS, leading to symptomatic neurosyphilis.[5] Most patients with neurosyphilis develop parenchymal manifestations such as tabes dorsalis or general paresis. However, 15%–30% of patients present with meningovascular syphilis, which occurs at an average of 7 years after the primary infection.[6] Inflammation of medium- and large-sized arteries is the most frequent subtype (Heubner endarteritis), and small vessel disease is known as Nissl endarteritis. The anterior circulation is more commonly affected than the posterior vasculature. Meningovascular syphilis is frequently preceded by prodromal symptoms such as malaise and headache.[7]

The incidence of syphilis has increased in the past decade,[8] and HIV co-infection is a risk factor for meningovascular syphilis, which is why such pathogens should always be suspected in patients with ischemic stroke who also exhibit risk factors for sexually transmissible infections.[5] The diagnosis is made by first confirming the presence of a syphilis infection using serologic treponemal tests such as fluorescent treponemal antibody test absorption test or EIA. A lumbar puncture should then be performed. A positive CSF venereal disease research laboratory test, pleocytosis or increased protein concentration (> 45 mg/dL) are consistent with neurosyphilis.[7] This patient's cachexia, aortitis and multifocal intracranial arteriopathy were all likely a result of a late syphilis infection. The vascular involvement may also have been potentiated by a long-standing, undiagnosed HIV co-infection.

One of the pitfalls of conventional intracranial vascular imaging techniques such as MR angiography, CT angiography or digital subtraction angiography is that contrast is confined to the vessel lumen, and various vasculopathies can present with similar luminal images. Vessel wall MRI of the intracranial arteries is an emerging MRI modality in which contrast-enhanced images obtained at high resolution allow for visualization of vessel wall characteristics, which can aid in differentiating atherosclerotic disease from other pathologies, such as primary CNS vasculitis or

Box 1: Conditions associated with an increased risk of ischemic stroke in young adults

Medications and substance use

- Oral contraceptives
- Alcohol use
- Cannabis
- Cocaine
- Amphetamines
- Opiates

Cardiac and structural associations

- Patent foramen ovale
- Congenital heart disease
- Valvulopathies
- Intracardiac tumours

Important nonstructural associations

- Migraine with aura
- Pregnancy
- Malignancy

Genetic and acquired thrombophilia

- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin III deficiency
- Antiphospholipid syndrome

Inflammatory vasculopathies

- Primary central nervous system vasculitis
- Systemic vasculitis

Noninflammatory vasculopathies

- Cervical artery dissection
- Intracranial artery dissection
- Radiation-induced vasculopathy
- Reversible cerebral vasoconstriction syndrome
- Moyamoya disease or syndrome

Infectious disorders

- Infective endocarditis
- Meningoencephalitis
- HIV
- Syphilis
- Tuberculosis

Monogenic disorders

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
- COL4A1 disorders
- Fabry disease
- Hereditary hemorrhagic telangiectasia
- Homocystinuria
- Marfan syndrome
- Sickle cell disease

RCVS. In 2017, the American Society of Neuroradiology published expert consensus recommendations regarding the clinical use of VW MRI,[9] which state that VW MRI, although technically challenging, is a "likely useful adjunct" in the evaluation of patients with intracranial atherosclerosis, vasculitis, RCVS, moyamoya disease, radiation-induced vasculopathy and arterial dissection. They describe distinctive vessel wall characteristics for various vasculopathies, such as the presence and pattern of vessel wall enhancement, with eccentric enhancement being typically associated with atherosclerotic plaque, and concentric enhancement suggesting an inflammatory process. In this patient, the concentric vessel wall enhancement of the basilar artery was consistent with arteritis. Histopathologic studies have shown that atherosclerotic plaques can develop concentrically, and the presence of concentric enhancement on VW MRI cannot reliably rule out atherosclerotic disease.[10] Moreover, apparent vessel wall enhancement does not necessarily correspond to pathology of the vessel wall itself, and other elements — such as an intraluminal thrombi, leptomeningeal disease or subacute ischemic strokes with peripheral parenchymal enhancement — can lead to false positives.[11] Consequently, such images should always be interpreted in the context of the clinical presentation. Despite these limitations, VW MRI may prove useful in the evaluation of patients with infectious vasculopathy of the intracranial arteries, although more research is needed to assess the technique's sensitivity and specificity in this context. In the presence of competing stroke etiologies, VW MRI allowed us to visualize signs consistent with meningovascular syphilis. One limitation of our workup was the absence of histopathologic correlation, and less common stroke etiologies, such as HIV-associated vasculopathy, could not be completely ruled out.

A large differential diagnosis should be considered in the assessment of young adults with ischemic stroke. Neurosyphilis is a well-recognized cause of stroke, and the rising incidence of syphilis underlies the importance of keeping a high index of suspicion for the disease, especially in patients with known risk factors. Vessel wall MRI may be a useful tool in the evaluation of patients with various intracranial vasculopathies, and can be helpful in the diagnosis of meningovascular syphilis.

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