

Medial medullary stroke due to neurosyphilis in a newly diagnosed HIV-positive man

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A 37-year-old white man presented to our hospital with a 4-day history of progressive dense right arm and leg weakness with associated hyperesthesia. The day prior to presentation, he had used intravenous methamphetamine, although he had not used methamphetamine recently, prior to the onset of symptoms. He denied facial weakness, dysarthria, dysphagia, visual symptoms, headache or neck pain.

He had no significant medical history and could not recall if he had ever undergone blood-borne virus or sexually transmitted infection screening. He reported infrequent IV methamphetamine use. His last sexual intercourse was 2 years ago, and he had both male and female partners.

On examination in the emergency department, he was haemodynamically stable with a temperature of 38.1°C. He had a dense right hemiplegia with 1/5 power in all muscle groups of the upper and lower limbs. Cranial nerve function was preserved, with no facial weakness or bulbar weakness, including no hypoglossal nerve paresis. The patient complained of hyperesthesia over the right upper limb. Proprioception was intact. Cortical and higher function testing were normal. He had a soft systolic murmur at the left sternal border but no peripheral stigmata of infective endocarditis.

Electrocardiogram showed sinus rhythm. Blood investigations, including full blood examination, C-reactive protein, renal and liver function tests and coagulation studies, were unremarkable (Table 1). A computed

Abstract

This case report presents the clinical record of a 37-year-old man who presented with a dense right hemiplegia, found to be caused by a left medial medullary stroke. The cause of the stroke was unclear, and bacterial endocarditis was initially suspected. However, he was ultimately found to have neurosyphilis on a background of undiagnosed human immunodeficiency virus and was treated with benzylpenicillin. This case report reviews the diagnosis of neurosyphilis and highlights the importance of considering neurosyphilis as a rare but important cause of stroke, especially given the increasing prevalence of syphilis in Australia.

tomography (CT) scan of the brain was normal, as was subsequent CT carotid and vertebral angiogram. After multiple sets of blood cultures were collected, he was commenced on empirical flucloxacillin, vancomycin and gentamicin for possible bacterial endocarditis, plus low-dose aspirin.

Magnetic resonance imaging of the brain showed an acute infarct in the left medial medulla (Fig. 1), which was considered atypical for thromboembolic cause. Transthoracic echocardiogram showed no embolic source, and there were no arrhythmias during cardiac monitoring. He had no further fevers. Seven sets of blood cultures all returned negative; however, he was continued on empirical endocarditis antibiotics while awaiting transoesophageal echocardiogram (TOE).

HIV serology performed on admission was positive (confirmed on western blot). Syphilis serology was also positive, with a rapid plasma reagin of 1:8 (Table 1). A lumbar puncture was performed to investigate possible neurosyphilis. Cerebrospinal fluid (CSF) examination showed raised protein (1.25 g/L) with mononuclear pleocytosis ($38 \times 10^6/L$). Microscopy (including India ink stain) was negative. This was considered in keeping with neurosyphilis, and he was commenced on specific treatment with ceftriaxone as the addition of 4-hourly benzylpenicillin to the empiric endocarditis antibiotic regimen was limited by dosing schedules.

TOE was subsequently negative for sources of emboli, excluding endocarditis as the cause of stroke. However, at this time (Day 4 of ceftriaxone therapy for presumed neurosyphilis), he developed a blanching erythematous rash over his neck and torso and low-grade fever of

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Table 1 Results of initial and subsequent investigations

Test	Result	Normal range
Admission investigation results		
White cells	$11.0 \times 10^9/L$	(4.0–11.0)
Neutrophils	$8.3 \times 10^9/L$	(2.0–7.5)
Lymphocytes	$1.8 \times 10^9/L$	(1.5–4.0)
CRP	3.2 mg/L	<5.0
Prothrombin time	11.9 s	(8.5–12.5)
Subsequent results		
HIV chemiluminescent microparticle immunoassay (CMIA)	Positive	
HIV RNA viral load	19 700 copies/mL	
CD4 count	$868 \times 10^6/L$	(>350)
Syphilis antibody screen (CMIA)	Detected	
TPPA (<i>Treponema pallidum</i> particle agglutination assay)	Positive	
RPR titre	1:8	
Hepatitis C virus antibody CMIA	Detected	
Hepatitis C RNA load	<12 IU/mL	
CSF		
Protein	1.25 g/L	0.15–0.45
Glucose	2.5 mmol/L	2.7–4.2
Leukocytes	$38 \times 10^6/L$ (100% MNC)	
Erythrocytes	$6 \times 10^6/L$	
Microscopy/Culture	Negative	
VDRL titre	8	
TPPA	Reactive	
Anti-nuclear factor antibody	Negative	
Antibodies to extractable nuclear antigens	Negative	
Cardiolipin IgG	Negative	
C3/C4	Normal levels	
Lupus anticoagulant	Negative	
Haemoglobin A1c (%)	5.9	4.3–5.7
Lipid studies	Normal	

CRP, C-reactive protein; HIV, human immunodeficiency virus; RPR, rapid plasma reagins; VDRL, venereal disease research laboratory.

37.7°C. It was unclear whether this was an allergic reaction to flucloxacillin, red man syndrome from vancomycin or a Jarisch–Herxheimer reaction. All antibiotics were ceased, an antihistamine was administered and the rash resolved within 24 h. Trypsin- and penicillin-specific IgE were negative. Given the importance of a benzylpenicillin-based regimen in this patient, the patient underwent an oral penicillin desensitisation protocol before being continued on benzylpenicillin of 1.8 g every 4 h for 15 days without further complications.

CSF syphilis serology was positive, including a venereal disease research laboratory (VDRL) titre of 8. This confirmed the diagnosis of neurosyphilis as the underlying aetiology of this patient's stroke, likely through a meningovasculitic process. Other significant investigations included positive hepatitis C serology, although viral load was undetectable, indicating cleared infection. CD4+ count was robust at $868 \times 10^6/L$. Other opportunistic and sexually transmitted infection screening was negative. He was commenced on emtricitabine, tenofovir and dolutegravir antiretroviral therapy. He was discharged to rehabilitation, where he proceeded to regain some power in his right lower limb and was able to mobilise independently. He regained minimal right upper limb power. He was planned for a repeat lumbar puncture in 3 months to monitor normalisation of the CSF pleocytosis and VDRL.

Discussion

Syphilis is known as the 'great imitator', and indeed, in this patient, the initial provisional diagnosis was an embolic stroke due to infective endocarditis. Blood-borne virus and sexually transmitted infection screening performed at presentation allowed the diagnosis of neurosyphilis to be reached in a timely manner.

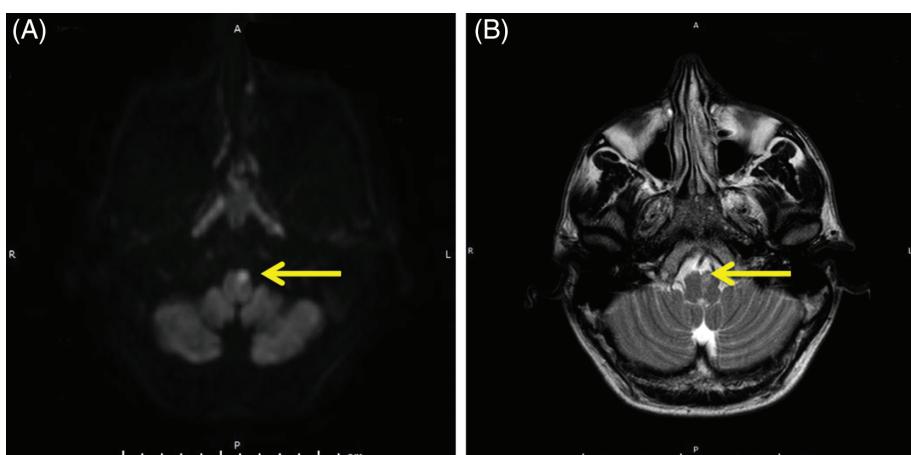


Figure 1 Magnetic resonance imaging of the brain showing a focus of restricted diffusion in the left medial medulla on axial diffusion-weighted image (A) corresponding to an area of high T2 signal (B), in keeping with an acute infarction (arrows).

Neurosypilis can occur at all stages of syphilis infection and refers to any central nervous system (CNS) invasion of *Treponema pallidum*.¹ The most common form of neurosypilis is general paresis, followed by syphilitic meningitis, meningovascular neurosypilis and tabes dorsalis.² Meningovascular neurosypilis is a manifestation of late neurosypilis and comprises meningeal inflammation and endarteritis of CNS arteries, which differs from parenchymatous neurosypilis (including general paresis and tabes dorsalis), which is primarily neurodegenerative. Endarteritis in meningovascular syphilis can affect both medium to large arteries (Heubner endarteritis) and small vessels (Nissl-Alzheimer endarteritis), and both types may lead to vascular occlusion, ischaemia and infarction.¹ Meningovascular neurosypilis most commonly involves the internal capsule, the middle cerebral artery, the carotid, the basilar artery, the posterior cerebral artery and cerebellar vessels.² Meningovascular syphilis typically occurs 4–7 years after initial infection,³ although in HIV-infected individuals, it may have an accelerated course.⁴

Meningovascular syphilis is a rare but recognised cause of stroke and may have an acute or subacute onset, often with prodromal neurological symptoms.⁵ Suspicion should be raised when a prodrome is present, the patient is young, risk factors for syphilitic infection are present, conventional stroke risk factors are absent or it is a cryptogenic stroke.⁶

The classic medial medullary syndrome (Dejerine syndrome) is a very rare stroke syndrome and consists of contralateral hemiparesis, hemisensory changes (proprioception and vibration) and involvement of the ipsilateral hypoglossal nerve. However, patients can present with significant variation in signs and symptoms due to the complex vascular and neuroanatomy of the region.⁷ Our patient likely had an ischaemic stroke of the anterior medial medulla, a region that contains the corticospinal tracts. The medial lemniscus (responsible for proprioception) and the nucleus for the hypoglossal nerve sit posteriorly in the medulla and were therefore spared. The territory of our patient's stroke was likely supplied by the anteromedial medullary artery, arising from the anterior spinal artery, which is uncommon in neurosypilis but has been described previously.⁸ This artery supplies the anterior medial region of the lower medulla and thus spares the medial lemniscus tracts and

hypoglossal nucleus. Sensory changes have been described in medial medullary syndrome, as well as other signs, including upbeat nystagmus, diplopia and ataxia.^{7,9,10} This likely occurs when nearby structures in the medulla are involved due to vascular anatomical variations or involvement of adjacent vessels.

If screening syphilis serology is positive, lumbar puncture should be performed to confirm the diagnosis of neurosypilis. If lumbar puncture is not possible, empirical treatment should be considered.¹¹ There is no adequate 'gold standard' to diagnose neurosypilis.¹ It is based on a combination of CSF analysis (protein and cells) and syphilis serology. Positive CSF-VDRL can confirm a diagnosis of neurosypilis but may only be positive in approximately one third of neurosypilis cases.¹¹ Furthermore, false positives can occur with blood-contaminated CSF. Conversely, CSF-TPPA (*T. pallidum* particle agglutination assay) is highly sensitive but poorly specific. When serological tests are negative, a presumptive diagnosis of neurosypilis can be made on the basis on an elevated CSF protein or monocytic pleocytosis.¹ The diagnosis of neurosypilis in HIV-infected patients with negative CSF serology can be difficult as HIV itself can cause an increased CSF protein and pleocytosis.¹² PCR detection of treponemal DNA in CSF is specific but poorly sensitive¹³ and, as such, is not included in the Centers for Disease Control and Prevention diagnostic guidelines.¹⁴

A retrospective Australian study found that syphilis serology was requested in only 27% of patients presenting with stroke, of which 4% were positive.¹⁵ Australia is currently experiencing two distinct syphilis epidemics, among urban men who have sex with men and in heterosexual Aboriginal people in regional and remote areas, predominantly across the Top End.¹⁶ Given the ongoing prevalence of syphilis, and its treatable nature, neurosypilis needs to be recognised as a rare but important cause of stroke.

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