

CASE REPORT

Meningovascular syphilis causing recurrent stroke and diagnostic difficulties: a scourge from the past

Sunil Munshi, Senthil K Raghunathan, Ileana Lindeman, Ashit K Shetty

Department of Stroke,
Nottingham University Hospitals
NHS Trust, Nottingham, UK

Correspondence to
Dr Sunil Munshi,
sunil512@gmail.com

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SUMMARY

We describe a case of a 49-year-old man who presented with recurrent strokes in the left middle cerebral artery territory, manifesting with dysphasia, higher cognitive deficits, motor deficits and subsequent infarcts in the right middle cerebral and anterior cerebral artery territories, manifesting with seizures, behavioural and social issues. A key issue of the case was the diagnostic difficulty faced by the physicians. 'Meningovascular syphilis' was subsequently confirmed and appropriate treatment was given but there was subsequent relapse with worsening of the symptoms. Multiple specialists were involved in the management, namely stroke team, neurologists, psychiatrists, infectious disease and multidisciplinary therapy teams. This case highlights the need to be vigilant to the resurgence of syphilis, a scourge from the past, as a cause of stroke, especially in individuals who have had exposure to affected people. It is easy to miss the diagnosis and mistake it for other conditions unless a detailed history is taken and appropriate investigations are conducted, with a low threshold for diagnosis.

BACKGROUND

The resurgence of syphilis in the modern era is of great public interest. Neurosyphilis manifests with a wide spectrum of symptoms and signs. Stroke, seizures and unexplained psychiatric symptoms are some of the manifestations. Tremendous clinical expertise is needed to diagnose syphilis when it affects the nervous system.

CASE PRESENTATION

A 49-year-old man was admitted with a subacute onset of speech difficulties with an inability to form words. His partner and parents found this extremely frustrating and brought him to the hospital. There was no history of any apparent vascular risk factors such as hypertension, diabetes, hypercholesterolaemia, recent head trauma or illicit drug use. He worked as a musician (guitarist) and had travelled to France, Spain and Portugal in the preceding 5 years. He was found to have an expressive dysphasia with subtle weakness of the right arm. Over the next 2 months, he developed gait apraxia.

INVESTIGATIONS

Cerebral imaging

An MRI was performed and confirmed an acute infarction in the left lenticulostriate territory (day 1, [figure 1](#)). With a diagnosis of ischaemic stroke,

he was started on aspirin (changed to clopidogrel after 2 weeks), along with atorvastatin 40mg. An MR angiogram on day 5 showed occlusion of the left middle cerebral artery (MCA) (day 5, [figures 2 and 3](#)). Seven weeks later, he was readmitted with a fresh recurrence of symptoms, and an MRI showed new infarcts in the right gangliocapsular region. In addition, a watershed infarct was seen in the right frontal cortical region, suggesting haemodynamic compromise of the anterior circulation due to steno-occlusive disease of the right MCA and anterior cerebral arteries (day 45, [figure 4](#)).

The patient's history was revisited. It was clear that he had exposure to multiple sexual partners over the last 5 years. Two years earlier, he had developed a lesion on his penis and a generalised rash that did not fade for almost 6 months while he was in Portugal. Further investigations were requested. His complete blood count, renal function, liver function test, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were all normal, and autoantibodies including antinuclear antibody, anti-neutrophil cytoplasmic antibody (ANCA) and anti-phospholipid antibody were negative. An HIV test was negative.

Carotid Dopplers and a two-dimensional echocardiogram were normal.

A lumbar puncture showed a mild elevation of protein in the cerebrospinal fluid (CSF; 850mg/L) and mild pleocytosis, mainly lymphocytes. CSF glucose was normal. Treponema serology of the CSF was strongly positive as evidenced by the rapid plasma reagin test (RPRT) and treponema pallidum particle agglutination test (TP-PA).

DIFFERENTIAL DIAGNOSIS

Recurrent ischaemic strokes localised to the MCA in a young man raises important diagnostic dilemmas. The irregularity and occlusion of the M2 segment of the MCA and subsequent involvement of the right side suggested a vasculitis of some type, most probably a condition affecting medium-sized or large-sized vessels. Common vasculitides of this type could be due to a number of reasons. The recurrence of symptoms and new infarcts pointed to an ongoing pathology. The history of multiple sexual partners, the primary lesion on his penis (of primary syphilis), and the rash and generalised lymphadenopathy (suggestive of secondary syphilis) prompted us to look for treponema pallidum as a possible cause of his symptoms.

At the Chapel Hill Consensus Conference, the primary systemic vasculitides were classified into



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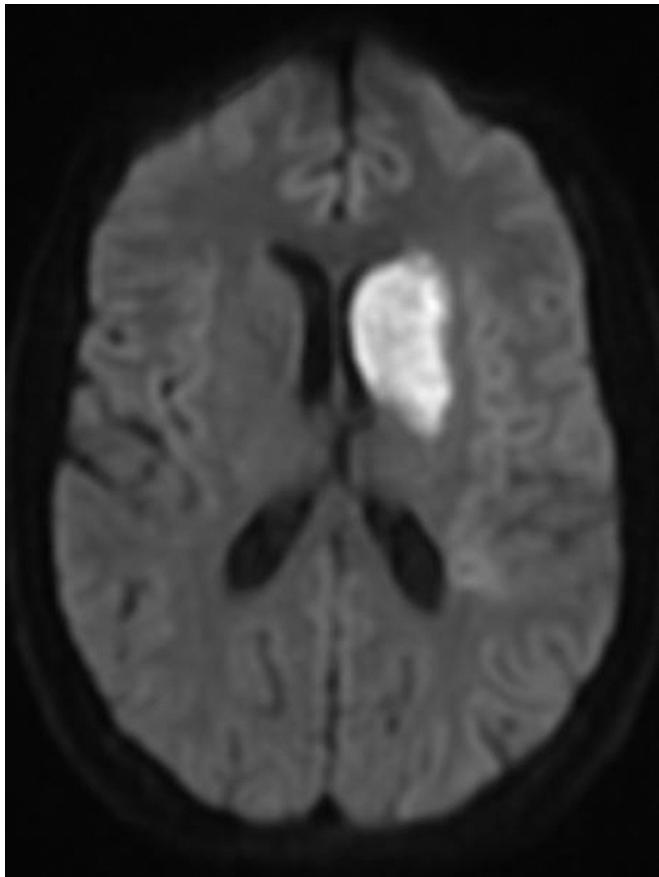


Figure 1 Diffusion-weighted MRI on day 1 showing the acute left lenticulostriate infarction.

three groups: those affecting mainly large-sized vessels, medium-sized vessels and small-sized vessels, respectively.¹ The original nomenclature of vasculitides was revised in 2012 as shown in [table 1](#).

Our patient did not have headache, jaw claudication or visual symptoms of giant cell arteritis (GCA). Blindness and stroke can occur in GCA which affects people over 50 years. CRP and ESR are usually elevated together with granulomas and giant cells on histology.² Takayasu arteritis (TA) affects people <50 years of age. Diagnosis is often delayed until the occlusive stage, causing ischaemic symptoms in limbs or stroke. Renovascular hypertension is common. Polyarteritis nodosa (PAN) can cause ischaemic stroke, haemorrhages and encephalopathy with or without seizures, usually preceded by systemic symptoms.³ Wegener's granulomatosis and Churg-Strauss syndrome affect small vessels. Our patient did not have small vessel disease. Behçet's disease is a chronic relapsing vasculitis affecting the venous system and occurs mainly in the Middle East, Far East and the Mediterranean. Oral and genital ulcers, uveitis and retinal vasculitis occur sometimes with neurological involvement. Neuro-Behçet's disease occurs in 30% with parenchymal involvement, stroke and headache; sinus thrombosis in 20% and neurological involvement may occur in 3% without mucocutaneous or ocular symptoms. Cogan's syndrome (similar to Behçet's disease) is associated with interstitial keratitis, sensorineural hearing loss and vasculitis producing large vessel aneurysms.³ Susac syndrome is associated with branch retinal artery occlusions, sensorineural hearing loss and neurological involvement. Cryoglobulinaemia-associated vasculitis can be associated with multi-organ involvement, lymphoproliferative disorders, hepatitis C



Figure 2 MR angiogram on day 5 showing the absence of left middle cerebral artery.

infection, hyperviscosity and cerebral infarction. Primary central nervous system vasculitis (PACNS) is rare, and it is important to exclude other causes of vasculitis that could mimic angiogram findings. Infectious diseases that resemble PACNS are neurosyphilis, borreliosis, rickettsial (typhus, etc), and viral diseases (varicella, cytomegalovirus, HIV) and bacterial endocarditis. It is reasonable to start steroids and immunosuppressants after infections have been excluded. Early stages of Moyamoya disease are often difficult to distinguish from other vascular lesions.³ Neurosarcoidosis occurs in 5%–15% of patients with sarcoidosis and can be severe and life-threatening. The following



Figure 3 MR angiogram of the circle of Willis on day 5 showing the absence of left middle cerebral artery.

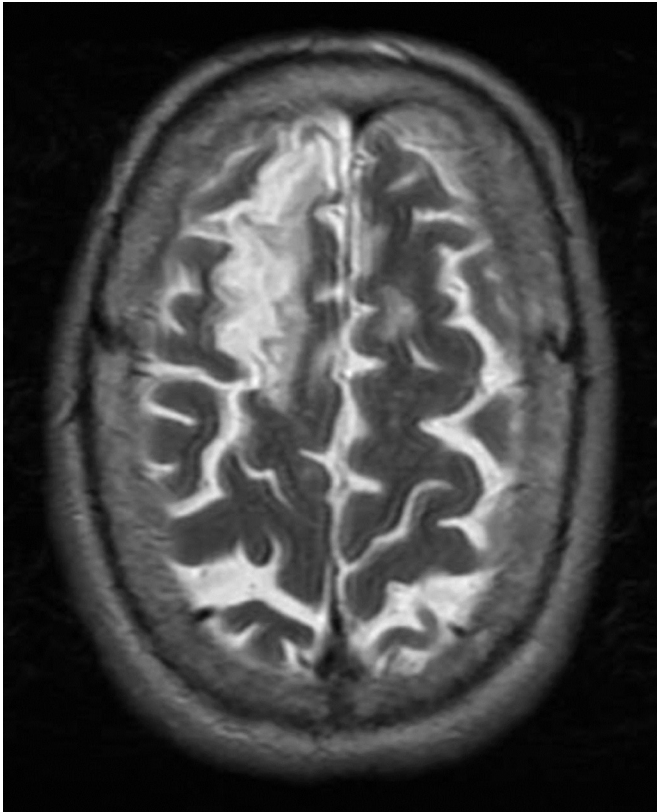


Figure 4 MRI on day 45 showing the watershed infarct in the right frontal cortex.

neurological abnormalities have been observed: papilloedema, cranial and peripheral neuropathy, mononeuropathy, myopathy, psychiatric disorders, cerebellar ataxia and hydrocephalus.

Our patient did not have the systemic features of GCA, TA, PAN, Wegener's granulomatosis, cryoglobulinaemia, neuro-Behçet's disease, neurosarcoïd, Churg-Strauss syndrome or other conditions like systemic lupus.

TREATMENT

The patient was managed on a hyperacute stroke unit and subsequently transferred to a rehabilitation unit. He received intensive speech therapy, physiotherapy and occupational therapy. Antiplatelet therapy in the form of aspirin 300 mg once daily was initiated and then changed to clopidogrel

75 mg once daily after 2 weeks on a long-term basis. He was initially given injection cyclophosphamide and methylprednisolone with a presumed diagnosis of primary CNS vasculitis. Subsequently when syphilis was confirmed, he was given Inj procaine penicillin 1.8–2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day for 17 days.⁴ This is in line with American Centers for Disease Control and Prevention (CDC) guidelines.⁵ He also received three additional doses of intramuscular benzathine penicillin (2.4 million units) over 3 weeks following completion of the initial antibiotic course. Antiepileptic medications were started following his seizures (initially levetiracetam which was later changed to lamotrigine). His partner also reported a rash suggestive of secondary syphilis, and she was treated as well. Both the patient and the partner received counselling and education about syphilis and sexually transmitted illnesses. He was discharged home with a care package and the support of the community rehabilitation team.

OUTCOME AND FOLLOW-UP

The patient showed a slow improvement in his day-to-day activities. His dysphasia and gait apraxia improved. One year later, he had a further relapse requiring further treatment and admission to the psychiatry unit.

DISCUSSION

Pathogenesis: Meningovascular syphilis (MVS) is one of the three symptomatic forms of neurosyphilis, itself a manifestation of tertiary syphilis. It accounts for approximately two-fifths of all cases of neurosyphilis and generally takes years to develop in an untreated patient after the primary infection. Peak occurrence is at 4–7 years, although this varies and stroke may occur at any time from the first month onwards.^{5–8} MVS is caused by an inflammatory obliterating endarteritis of the blood vessels supplying the leptomeninges, brain and spinal cord.^{5,9} Pathological changes eventually lead to luminal obliteration (and rarely aneurysm development) and subsequent distal neural tissue infarction.⁵ This creates a combined syndrome of chronic syphilitic meningitis, cerebrovascular and/or myelovascular events.⁵ The disease more commonly affects large-sized and medium-sized vessels—known as Heubner's arteritis—although small vessels may also be involved—known as Nissl-Alzheimer's arteritis.⁵ Presentation in the preantibiotic era, syphilis was a common cause of stroke.⁸ Today, there is a high misdiagnosis rate of MVS, both due to the decline in the prevalence of syphilis in the antibiotic era and due to its presenting symptoms mimicking other stroke aetiologies that are more common nowadays—such as atherosclerotic disease or vasculitides.^{4,8,10} A retrospective study of 149 patients with neurosyphilis found that the rate of misdiagnosis of neurosyphilitic ischaemic stroke was as high as 80%.¹⁰ Around a quarter of patients with MVS have prodromal symptoms, likely due to concomitant meningitis—intermittent headaches, vertigo, insomnia or behavioural changes.^{5,8,11} These may occur for days,¹¹ weeks or even months prior to the ischaemic event.⁵ The presentation of the ischaemic event itself depends on the vascular territory involved—most commonly the MCA.^{4,5,11} Thus, the most likely manifestations include contralateral hemiplegia, hemianaesthesia, homonymous hemianopia and aphasia.⁸ Less common locations for the arteritides are the basilar⁸ or anterior spinal arteries.¹¹

Table 1 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides¹

Large-vessel vasculitis	Takayasu arteritis, giant cell arteritis.
Medium-vessel vasculitis	Polyarteritis nodosa, Kawasaki disease.
Small-vessel vasculitis	Anti neutrophil cytoplasmic antibody associated vasculitis; immune complex.
Variable-vessel vasculitis	Behçet's disease, Cogan's syndrome.
Single-organ vasculitis	Cutaneous leucocytoclastic angiitis, cutaneous arteritis, primary central nervous system vasculitis, isolated aortitis, others.
Vasculitis associated with systemic disease	Lupus vasculitis, rheumatoid vasculitis, sarcoid vasculitis, others.
Vasculitis associated with probable aetiology	Hepatitis C virus-associated cryoglobulinaemic vasculitis, hepatitis B virus-associated vasculitis, syphilis-associated aortitis, drug-associated immune complex vasculitis, cancer-associated vasculitis, others.

Diagnosis

As there is no gold-standard diagnostic test for neurosyphilis or MVS, diagnosis relies on clinical judgement and laboratory tests.⁸ First, the stroke-focused history must include an inquiry into prodromal symptoms and potential risk factors or history of sexually transmitted diseases.⁵ The peak age presentation of neurosyphilis and MVS varies in the literature, with a range between the late fourth and the early seventh decades, with males more frequently involved.^{6,7} MRI can confirm acute infarct.⁵ Angiography shows segmental, concentric steno-occlusive arteriopathy, but only in medium and large-vessel disease, and this finding is shared with central nervous system (CNS) arteritides of other vasculitic origin.⁵

Laboratory testing for neurosyphilis is usually undertaken in steps: first, to establish if there is any suggestion of syphilis; second, to confirm syphilis; and third, to investigate if there is evidence of the disease in the nervous system. In the first step, serum non-treponemal (or cardiolipin) tests are used—in particular, the RPR or venereal disease research laboratory test (VDRL). These lack specificity for treponemal infection and are poorly sensitive in early and late syphilis. Nevertheless, if they are positive, a titre is estimated, with values greater than 1:8 suggestive of syphilis infection.⁵ The second step involves confirming the presence of syphilis. Several tests may be used, most commonly the highly sensitive fluorescent treponemal antibody absorption test (FTA-Abs).⁵ Other tests include treponema pallidum haemagglutination assays (or microhemagglutination assay commonly known as MHA-TP), TP-PA or the toluidine red unheated serum test.

Once syphilis is diagnosed, it is important to determine whether neurosyphilis is also present, as the usual treatment for syphilis does not achieve treponemicidal levels beyond the blood–brain barrier.^{5,8} This is usually done if VDRL titres (from step one) are elevated, with cut-offs of 1:8 or 1:32 generally being used. In addition, experience with patients coinfecting with HIV suggests that prevention of neurological complications from syphilis requires both appropriate treatment and a robust immune system.⁸ Hence, this step is particularly important if there is HIV coinfection. Cerebrovascular fluid (CSF) investigation is the mainstay of this diagnostic step. Elevated leucocyte and protein counts suggest CNS infection; however, they are less severe in MVS than in acute meningitis. Lymphocytic pleocytosis is usually between 10 and 100 cells/ μ L and protein concentration between 100 and 200 mg/dL.⁶ In addition to these tests, non-treponemal or treponemal CSF testing can be undertaken which is highly specific but very poorly sensitive, hence not excluding the disease if they are negative. Most commonly, CSF-VDRL is used as CSF FTA-Abs is very expensive.⁵

Management

The management of MVS includes antibiotic treatment as for neurovascular syphilis and stroke-specific treatment. If the time window permits and there are no contraindications, it may be warranted to use recombinant tissue plasminogen activator for thrombolysis.⁹ Long-term antiplatelet agents are indicated for prevention, especially if other stroke risk factors are present.⁵ It is important to institute antibiotic treatment as urgently as possible, as delaying it can lead to further occlusive events. In addition, a wrong diagnosis may lead to instituting treatment deleterious to the immune system of patients with neurosyphilis, such as steroids and/or immunosuppressants for vasculitides (as happened in this case). The current UK

national guidelines for syphilis management recommend using procaine penicillin G 1.8–2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day for 17 days. This is in line with the CDC guidelines.⁵ Alternatively, benzylpenicillin 18–24 million units daily can be used, given intramuscularly as three divided doses every 4 hours, for 17 days. The CDC recommends this regimen to be given intravenously. Other alternatives include doxycycline, amoxicillin plus probenecid or ceftriaxone, in non-anaphylactic penicillin allergy.⁴ Clinicians often give 1–3 additional doses of intramuscular benzathine penicillin (2.4 million units) over 3 weeks following completion of the initial antibiotic course.^{5,8} Follow-up entails monitoring CSF parameters and cerebrovascular health. It is recommended to repeat CSF analysis every 6 months until the leucocyte count is normal, with treatment repeated if this does not happen within 2 years.⁵ Changes in CSF-VDRL and CSF protein occur more slowly than changes in leucocyte counts,⁵ and treponemal tests may remain positive for life despite effective treatment and hence are not routinely monitored. Follow-up imaging (angiography) is employed to assess the status of large vessel cerebral vasculature, and this may also inform the continued need for antiplatelet therapy in an asymptomatic, successfully-treated patient.⁵

Learning points

- ▶ The resurgence of syphilis in the modern era is of great public interest.
- ▶ Neurosyphilis is a great 'mimicker' and can present with a wide array of signs and symptoms.
- ▶ Taking a detailed history in susceptible individuals is paramount.
- ▶ Meningovascular syphilis should be considered as a diagnostic possibility in unexplained strokes in vulnerable individuals.
- ▶ Prior to giving toxic immunosuppressive therapy for presumed primary angiitis of the nervous system or other vasculitides, infective aetiologies should be excluded.

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