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ACUTE ISCHAEMIC STROKE IN THE CONTEXT OF NEUROSYPHILIS: HOW DOES ANTIBIOTIC THERAPY HELP, AND WHEN SHOULD IT BE GIVEN?

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ABSTRACT

Introduction: Neurosyphilis (NS) refers to a central nervous system infection caused by *Treponema pallidum*. In recent years, there has been an increasing incidence of syphilis; however, NS is uncommon compared to the era before the discovery of penicillin. Manifestations are usually non-specific, ranging from asymptomatic cases to syphilitic meningitis, meningovascular syphilis, general paresis and tabes dorsalis. Meningovascular syphilis can cause an inflammatory arteritis of cerebral arteries, leading to vascular occlusion and cerebral infarction.

Case description: We report a case of an ischaemic stroke in a patient with several vascular risk factors, presenting with right hemiparesis, hemihypesthesia and dysarthria. Initial computed tomography with angiography of the head and neck was normal; however, magnetic resonance imaging of the brain revealed a thalamic and internal capsule infarct. Serum *T. pallidum* antibodies were positive, as well as a rapid plasma reagin test. Cerebrospinal fluid analysis confirmed the diagnosis of neurosyphilis, and the patient was treated with ceftriaxone for 14 days due to a penicillin allergy.

Discussion and conclusion: Although there is a high prevalence of stroke in patients with NS, this condition is typically underdiagnosed. Untreated NS carries a higher risk of stroke recurrence compared to other risk factors. Therefore, early diagnosis and treatment are essential. This case highlights the importance of considering NS in stroke victims, even in older patients with several additional vascular risk factors, to prevent recurrence and other complications.

KEYWORDS

Neurosyphilis, meningovascular syphilis, arteritis, stroke, acute cerebrovascular event

LEARNING POINTS

- Neurosyphilis (NS) can occur at any stage of syphilis infection, and it can be asymptomatic or symptomatic, presenting as syphilitic meningitis, meningovascular syphilis, general paresis or tabes dorsalis.
- Ischaemic strokes are a frequent complication of NS, occurring in 14% of the cases. However, only 19% of the cases are correctly diagnosed.
- NS should be considered as a potential cause of stroke, even in older patients with several other vascular risk factors. This is essential to prevent future strokes, as well as dementia and other complications.

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INTRODUCTION

Syphilis is a sexually transmitted infection caused by the bacteria *Treponema pallidum*. If left untreated, it can advance through various stages including primary, secondary, latent and tertiary syphilis[1]. Despite the recent increase in the incidence of syphilis in Western Europe, neurosyphilis (NS) is an uncommon presentation compared to the era before penicillin[2]. NS can occur at any stage of the infection, as the *T. pallidum* infiltrates the central nervous system shortly after the primary infection[2]. It can be asymptomatic or symptomatic, presenting as syphilitic meningitis, meningovascular syphilis, general paresis or tabes dorsalis[2]. Ischaemic strokes are a frequent complication of NS, occurring in 14% of the cases[1]. We present a case of NS contributing to an ischaemic stroke in a woman with other cerebrovascular risk factors.

CASE DESCRIPTION

A right-handed 63-year-old female was transported to the emergency department by the pre-hospital emergency team with complaints of three hours' duration of right-side weakness and numbness, as well as slurred speech that improved during transportation. She had a past medical history of traumatic brain injury in 2012 with a small right frontal lobe haemorrhage, essential arterial hypertension, cigarette smoking, being overweight (body mass index of 27.2 kg/m^2), depression and penicillin allergy. Despite frequently reporting self-measured blood pressures above 140/90 mmHg, she was only medicated with mirtazapine, due to a lack of medical accessibility. No other prior medical or family history was known.

On admission, she had a National Institute of Health Stroke Scale (NIHSS) score of 4, significant for mild right hemisensory loss, right upper and lower extremity drift, and mild dysarthria. Her heart rate was 95 beats/minute and regular, blood pressure was 173/81 mmHg and transcutaneous oxygen saturation was 98% without supplementary oxygen. No other alterations on physical and neurological examinations were found.

Initial laboratory analysis had no significant alteration, and the electrocardiogram revealed a normal sinus rhythm. A computed tomography (CT) scan of the head revealed no abnormalities (Alberta Stroke Program Early CT Score (ASPECTS) – 10 out of 10) *(Fig. 1)*. After contrast injection, the CT angiography of the head and neck showed no large vessel occlusion or stenosis of the main vasculature. Fibrinolytic therapy was not performed due to the patient's past medical history of cerebral haemorrhage. The patient was admitted to the stroke unit and medicated with 100 mg/day of acetylsalicylic acid and 80 mg/day of atorvastatin.

A magnetic resonance imaging (MRI) of the brain was performed showing a left thalamic and internal capsule infarct *(Fig. 2)*. The transthoracic echocardiogram, carotid duplex ultrasound and transcranial Doppler were unremarkable. A more detailed laboratory analysis revealed a high-density lipoprotein of 27 mg/dl, a low-density lipoprotein of 184 mg/dl and a glycated haemoglobin of 6.5%. Serologies were negative for human immunodeficiency virus, hepatitis C virus and hepatitis B virus. However, *T. pallidum* antibodies (IgG + IgM) were positive, with a rapid plasma reagin (RPR) titre of 1:256. After lumbar puncture, the cerebrospinal fluid (CSF) analysis showed a white blood cell count of 164/mm3, mainly lymphocytes without blood contamination, elevated protein levels of 75 mg/dl (reference range: 15–60 mg/dl), and a positive venereal disease research laboratory (VDRL) test with a titre of 1:4. These findings confirmed the diagnosis of NS. After 2 days in the stroke unit, the patient's neurological deficits began to improve, with only mild right hemisensory loss remaining (NIHSS 1) on the third day. Due to a past medical history of penicillin allergy, on the fourth day the patient was started on intravenous ceftriaxone 2 g/day.

Figure 1. Head CT at hospital admission showing no abnormalities (ASPECTS 10 of 10).

The patient was discharged from the hospital medicated with mirtazapine, metformin, atorvastatin, perindopril, amlodipine, and dual antiplatelet therapy for 28 days, maintaining single antiplatelet therapy after this period. Ceftriaxone was administered for 14 days at the patient's home, with support from the domiciliary hospitalisation team. One month after the event, the patient was observed at a stroke medicine consultation, and a complete resolution of all neurologic deficits was seen. An infectious disease consultation was scheduled; however, she missed several appointments, and the NS follow-up was lost.

DISCUSSION

Meningovascular syphilis is a form of NS and can occur in 0.3–2.4% of all patients with syphilis and in 38.5% of patients with symptomatic NS[1]. It is characterised by an

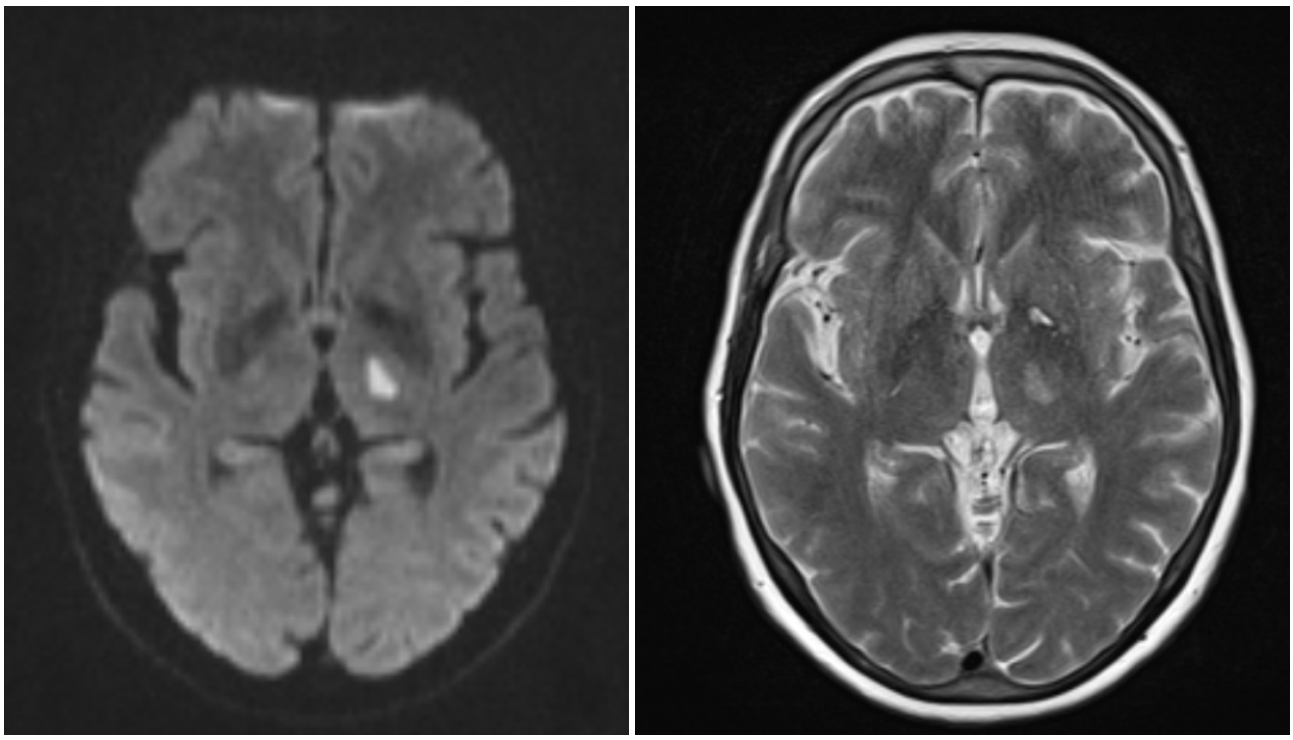

Figure 2. Brain MRI (diffusion weighted imaging [left] and T2 weighted [right]) showing left thalamic and internal capsule infarct.

inflammatory obliterative endarteritis of cerebral arteries and can have two types of presentation: Heubner arteritis, the most frequent type, affecting large and medium-sized arteries, and Nissl-Alzheimer arteritis, involving smaller vessels[3]. Both arteritis can lead to vascular occlusion and cerebral infarction[3]. *T. pallidum* also interacts with platelets and activates them, ultimately contributing to vessel occlusion and ischaemic strokes[4].

In patients with syphilis, a serum RPR titre ≥ 1:32 increases the risk of asymptomatic NS by five times, making it an independent predictor for this complication[5]. Our patient had an RPR titre of 1:256, therefore a lumbar puncture was an essential procedure to assess the presence of NS. The typical CSF findings in NS are pleocytosis and elevated protein count[2]. A reactive CSF-VDRL (without blood contamination) in a patient with neurologic signs or symptoms is diagnostic of NS[2]. Our patient's CSF sample had pleocytosis, elevated protein count and a VDRL titre of 1:4, in the absence of blood, confirming the diagnosis of NS.

We lack histological proof that NS was the primary cause of the stroke in our patient, rather than other vascular risk factors. Nevertheless, it should be regarded as a co-contributor to cerebral small vessel disease and treated accordingly. Similar to late NS syndromes, there is no clear evidence of improvement in stroke symptoms after NS treatment, particularly in cases of established ischaemic neuronal death[2]. Although our patient had a spontaneous early improvement, which is fairly common in lacunar strokes, NS treatment remains essential to halt arteritis progression[2,6].

Parenteral penicillin is the most effective and the first-line treatment for NS. However, in patients with penicillin allergy, ceftriaxone 2g/day for 14 days is a safe choice due to a negligible risk of cross-allergy[2]. During the initial 24 hours of neurosyphilis treatment, Jarisch-Herxheimer reaction can occur in up to 11% of patients[7]. Apart from the typical symptoms of fever, chills, myalgia, headache, hyperventilation, haemodynamic instability and leukocytosis, two reports in the literature suggest a potential link to ischaemic strokes[7]. While this exceedingly rare complication should be considered in neurosyphilis treatment, it should not serve as a reason to withhold antibiotic therapy.

CONCLUSION

Despite the high prevalence of stroke in patients with NS, only 19% of the cases are correctly diagnosed[1]. This can be explained by the presence of multiple vascular risk factors, leading physicians to overlook other causes and not test patients for syphilis. However, when compared with other risk factors, untreated NS has a higher risk of stroke recurrence[1]. Although antibiotic therapy may not reverse stroke symptoms, it can halt arteritis progression and prevent future strokes, as well as dementia and other complications. This case report highlights the importance of considering NS as a cause of stroke, even in older patients with several others vascular risk factors.

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