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Case Report

Neurosyphilis presenting with focal middle cerebral artery stenosis and acute ischemic stroke: A case report ☆

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ABSTRACT

Despite widespread screening and active management of syphilis infection, the rate of secondary and tertiary syphilis has increased over the past decade in the United States, especially with human immunodeficiency virus co-infection. We report a case of ischemic strokes in the middle cerebral artery (MCA) territory with focal stenosis of the left M1 segment of the MCA resulting from neurosyphilis with manifestation of subacute intermittent right-sided hemi-body numbness and transient word finding difficulties in a young adult with no prior known history of syphilis or significant cerebrovascular risk factors. A diagnostic cerebral angiogram was done which was initially concerning for possibility of reversible cerebral vasoconstriction syndrome (RCVS). The serum *Treponema pallidum* RPR testing resulted positive (1:32 titer) as well as subsequent reactive cerebrospinal fluid (CSF) VDRL test (ratio, 1:8). The patient was treated with intravenous ceftriaxone as well as verapamil and recovered without any residual deficits. To the best of our knowledge, this is the first reported evidence of possible RCVS in a case of neurosyphilis and related ischemic stroke. This case underscores the importance of evaluation for syphilis in young patients with fewer known vascular risk factors, who present with an ischemic stroke. Given the higher rates of stroke recurrence in neurosyphilis relative to few other stroke risk factors, early diagnosis, and treatment is furthermore essential to prevent disease progression.

Introduction

Syphilis is a sexually transmitted disease (STD) that usually progresses into 4 stages if left untreated, with widespread involvement of all organ systems [1]. The incidence rates of secondary and tertiary syphilis have been on the rise in the 21st century, especially in patients with human immunodeficiency virus (HIV) coinfection [2]. Neurosyphilis is a form of tertiary syphilis, and neurologic manifestations may well be the first

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presenting symptoms of an undetected syphilis infection. The diagnosis of neurosyphilis is often challenging given the wide range of atypical presentations and being known as a "great mimicker" of other diseases [3–5]. It is unusual in young patients without known atherosclerosis risk factors to develop intracranial stenosis, particularly given the rising incidence of known vascular risk factors [6]. The diagnosis and differentiation between non–atherosclerotic vasculopathies (NAV) such as neurosyphilis & reversible cerebral vasoconstriction syndrome (RCVS) are a clinical dilemma, and NAV accounts for 15% of strokes in adults [7]. The co-occurrence of RCVS and neurosyphilis has not been demonstrated in the past. We describe a case of vasculopathy from neurosyphilis contributing to ischemic strokes of the MCA territory from symptomatic intracranial stenosis in a young woman without prior known history of syphilis or any cerebrovascular risk factors. Informed consent was obtained by the patient for the current presentation of case.

Case presentation

A 29-year-old woman with no significant past medical history except for intermittent headaches and being an everyday smoker (about half pack per day) presented with a new onset of subacute intermittent right-sided hemi-body numbness and recurrent transient word finding difficulties. She was not on any daily home medications and only had an intrauterine device (IUD) without being on any oral contraceptive medications. On further questioning, she was found to have multiple sexual partners, and last had a negative syphilis screen about 6 years prior to the current admission. Her blood pressure upon arrival to the emergency room was 138/50 mm Hg (systolic blood pressure during hospitalization ranged from 90s to 130s mm Hg). The initial neurologic examination revealed expressive aphasia with associated dysarthria and decreased fine touch sensation over right forearm without any signs of light near dissociation. Initial non–contrast head computed tomography (CT) scan revealed ill-defined hypodensities in the left posterior parietal lobe with hemorrhagic transformation and a few ill-defined hypodensities in the left frontal lobe as well (Fig. 1). CT angiogram head and neck was notable for focal moderate to severe stenosis of the left M1 segment of the middle cerebral artery (MCA) (Fig. 1). Brain magnetic resonance imaging (MRI) with and without contrast demonstrated numerous foci of diffusion restriction involving white matter as well as gray matter of the left cerebral hemisphere including left centrum semiovale, parietal-occipital region, anterior temporal region, as well as punctate foci involving frontal and parietal gyri show correlating FLAIR hyperintensity, suggestive of ischemic infarct (Fig. 2). There was T1 hyperintensity associated with the left parietal white matter and left occipital lesion suggesting subacute infarct with hemorrhagic transformation. A left basal ganglia focal enhancing lesion with T1 hyperintensity and without diffusion restriction was observed (Fig. 2). Routine stroke workup including transthoracic echocardiogram with bubble study, 48-hour Holter monitoring, laboratory investigations such as complete blood count (CBC) with differential, serum electrolytes, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and liver function testing were all within normal limits. Given the patient's young age and unusual stroke, a potential vasculopathy vs vasculitis etiology was suspected, and the following labs were also ordered: HIV and Lyme disease antibody screening, antineutrophil cytoplasmic antibodies (ANCA), proteinase 3 (PR3), myeloperoxidase (MPO), and anti–double-stranded DNA antibodies were all negative. Given her age and complaints of headaches, she was started on verapamil out of concern for reversible cerebral vasoconstriction syndrome (RCVS). As the etiology of her stroke was unclear, she was evaluated further with a diagnostic cerebral angiogram which was notable for presence of partial reversibility of her focal left M1 segment stenosis following 10 mL of intra-arterial verapamil injection (Fig. 3). This finding was initially concerning for the possibility of RCVS and because of this, she was continued on oral verapamil therapy.

Her *Treponema pallidum* RPR testing resulted positive with a 1:32 titer. To assess the neurosyphilis, cerebrospinal fluid (CSF) study was subsequently done which showed elevated protein level of 74 mg/dL (normal range, 15-45 mg/dL), increased white cell count (48 cells/mm^3) with lymphocytic predominance, and normal glucose level of 45 mg/dL (50-80 mg/dL). CSF VDRL was reactive with a ratio of 1:8. CSF culture showed no growth and there were no oligoclonal bands or abnormal cells present. Based on the positive serum and spinal fluid serology and angiographic findings in the setting of acute-subacute cortical infarcts, a diagnosis of neurosyphilis was made. She was started on intravenous ceftriaxone due to previous history of penicillin allergy.

Outcome and follow up

Patient had complete resolution of symptoms with NIHSS 0 at the time of discharge and patient was back to her normal functioning (Modified Ranking scale 0). She was discharged home with infectious disease and neurology follow-up. She completed intravenous ceftriaxone for a total of 14 days, continued verapamil 40 mg twice daily, and was discharged with a 30-day cardiac event monitor. A repeat head CT angiography was performed 86 days after her initial study which redemonstrated a slight improvement, however, continued focal moderate stenosis of the left distal M1 (Fig. 1).

Discussion

Neurosyphilis refers to the infection involving the CNS by *Treponema pallidum* [3]. This is usually seen in tertiary syphilis and is often 5-7 years from the time of initial syphilis infection. Clinical presentations in neurosyphilis range from asymptomatic infections to neuropsychiatric manifestations which are the most common manifestations [8]. The extent of neuroinvasion can include the parenchyma (as seen in general paresis and tabes dorsalis), spinal cord, meninges, and vessels [8,9]. Classical CSF findings of neurosyphilis include a CSF pleocytosis with an elevated protein count. A CSF VDRL which has a

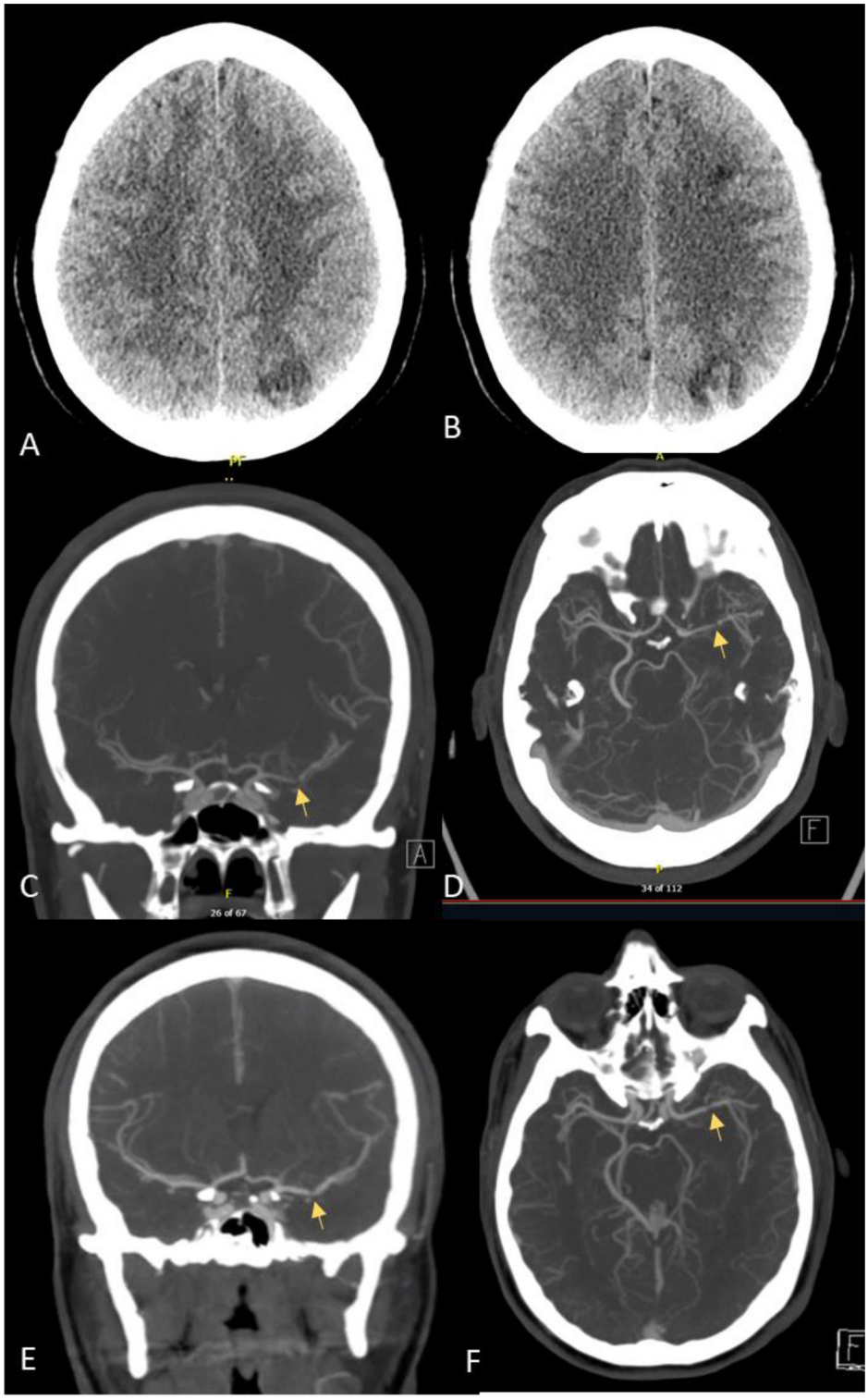

Fig. 1 – Axial non–contrast CT head (A and B) showing hypodensities in the left posterior parietal lobe with hemorrhagic transformation and left frontal lobe. Coronal and axial CT angiograms (C and D) on initial presentation showing focal moderate to severe stenosis of the left M1 of the middle cerebral artery (MCA) and 86 days later (E and F) showing moderate stenosis of left M1 (improved from initial image, yellow arrows) (Color version of the figure is available online.)

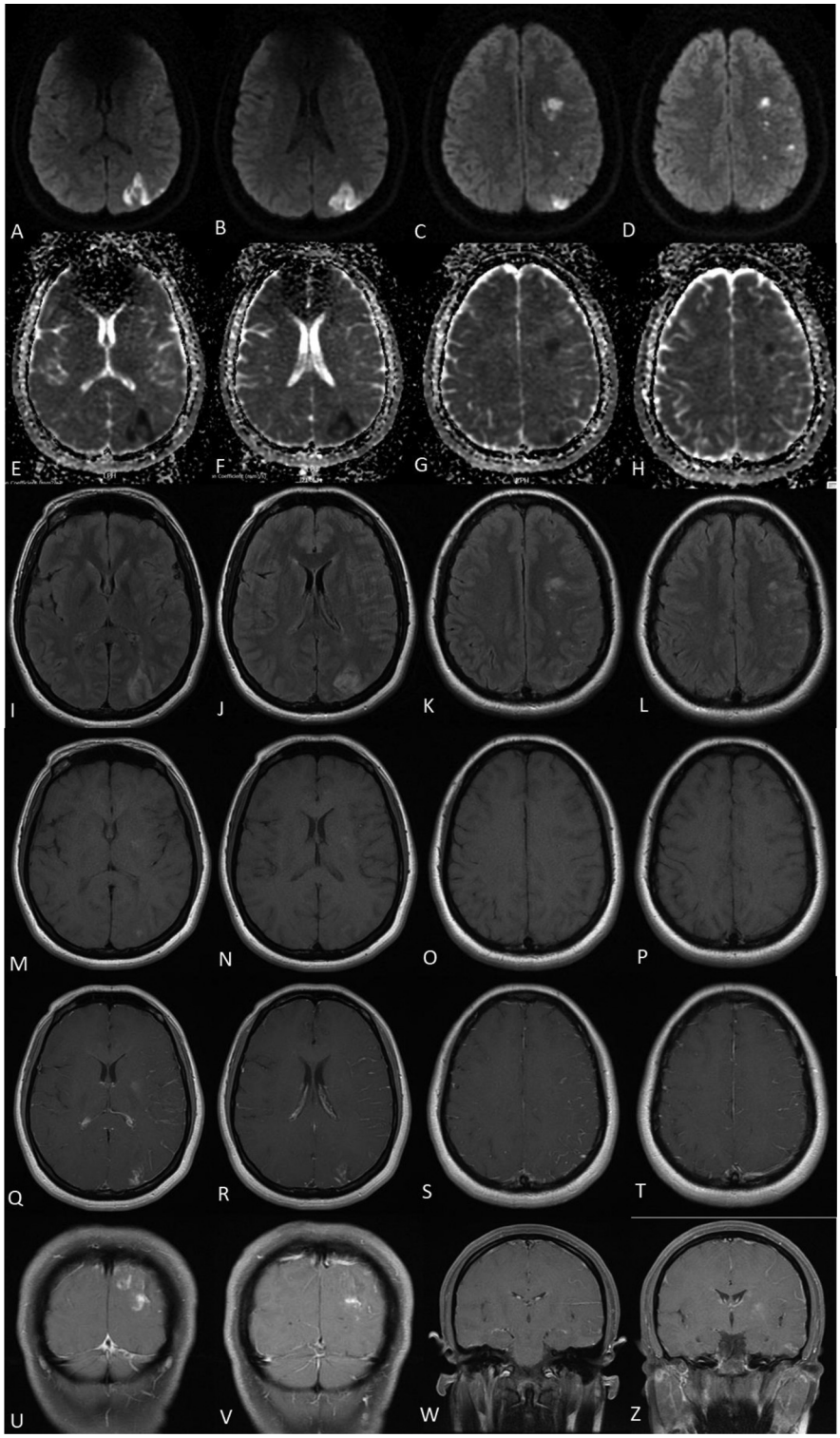

Fig. 2 – Axial DWI (diffusion weighted imaging) (A-D), axial ADC (apparent diffusion coefficient) (E-H), axial T2 FLAIR (I-L), axial T1 pre- (M-P) and post-contrast (Q-T) as well as coronal T1 post-contrast (U-Z) brain MRI from day of admission showing numerous foci of ischemic infarcts involving left cerebral hemisphere, a few of them are in subacute stage and show enhancement and hemorrhagic transformation. There is also a left basal ganglia focal enhancing lesion with T1 hyperintensity and without diffusion restriction (indeterminate in nature).

Fig. 3 – Diagnostic cerebral angiogram showing a distal left M1 middle cerebral artery (MCA) segment stenosis (A) with partial improvement in caliber after administration of 10 mg of intra-arterial Verapamil (B) (red arrows) (Color version of the figure is available online.)

high specificity, is virtually diagnostic in these circumstances in the absence of blood contamination of CSF which may result in false positives [10,11]. Due to low sensitivity of this test, further testing with CSF FTA-ABS testing is recommended if the VDRL is negative, and there is still a high clinical suspicion [12].

Meningovascular Syphilis has largely been considered an endarteritis associated with large most frequent MCA followed by basilar artery and small to medium intracranial vessel involvement. This is usually characterized by thinning of the media, inflammation of the adventitia with lymphoplasmocytic infiltrate, and fibroblastic proliferation of intima. This may result in subsequent cerebral artery occlusions due to thrombosis and vessel occlusion that may lead to ischemic strokes [9,13,14]. Strokes can occur in approximately 15% of untreated patients with neurosyphilis [14]. *Treponema pallidum* has been demonstrated to interact with platelets that results in activation of the platelets and aggregation with the ultimate scope of opening blood brain barrier and parenchymal invasion [15]. Strokes can occur in approximately 15% of untreated patients with neurosyphilis [14], in which the MCA territory is most affected followed by the basilar artery [16,17]. The recurrence of stroke in untreated neurosyphilis is higher than other common stroke risk factors, eg, atrial fibrillation with a high CH2DS2VASc score of 8 which is attributed to a 6.7% annual stroke risk [18]. It is demonstrated that in patients with previously unknown syphilis infection, a serum RPR titer $\geq$ 1:16 was an independent marker of the degree of intracranial stenosis [19].

It is likely that similar pathogenic mechanisms resulting from treponemal invasion of the cerebral vasculature may contribute to our case with focal stenosis of the left MCA. While on the repeat CT angiography performed ~3 months after the initial CT angiography there was no evidence of progressive vasculopathy, the degree of focal intracranial stenosis was slightly improved after treatment with ceftriaxone. Effective management with combination of both verapamil in this case due to initial concern for cerebral vasospasm as well as intravenous ceftriaxone helped prevent disease progression. To the best of our knowledge, this is the first reported evidence of possible RCVS in a case of neurosyphilis. This case underscores the importance of evaluation for syphilis in young patients with fewer known vascular risk factors, who present with an ischemic stroke.

Concluding remarks

A high degree of clinical suspicion should be maintained when evaluating young patients with stroke-like-symptoms in the absence of vascular risks factors. A high-serum RPR titer in the context of neurosyphilis is an independent marker for intracranial stenosis. Neurosyphilis has higher rates of stroke recurrence than a few other stroke risk factors. Given recent trend for increase in incidence rates of tertiary syphilis; early diagnosis and prompt treatment is furthermore essential to prevent disease progression to more long-term adverse outcomes such as dementia, paralysis, and death.

Informed consent and patient details

The written informed consent was obtained from the patient for this case report and is retained by the authors. It will be provided if the journal request for verification. Notably, all the data including imaging results are provided anonymously throughout the paper.

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