

Stroke in a young patient with neurosyphilis and HIV

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Abstract

Syphilis has long been known as the great imitator. Its heterogeneity can manifest in the form of meningitis, space occupying gummas, vasculitis, strokes, cranial neuropathies, myelopathy, dementia, and seizures. The incidence has been rising with each year, mainly in men who have sex with men accounting for 83% of cases. With the coexistence of immunocompromised states, especially HIV (human immunodeficiency virus), the usually chronic and insidious course of tertiary neurosyphilis can be accelerated. Stroke can occur as a result of neurosyphilis in its meningo-vascular form, and the likelihood of this increases with HIV co-infection, especially in high-risk groups such as intravenous drug users and men who have sex with men. Here, we discuss a case of a young man who presented with an ischemic stroke found to have neurosyphilis and HIV and consider the management of these co-morbid conditions.

Keywords

Bacterial disease, HAART, HIV, homosexual, screening, syphilis

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Case

A 28-year-old, right-handed man presented after waking up to right hemiparesis. He denied any prodrome of headache, vision changes, neck pain, stiffness, fever, or rash. He had a similar episode several months ago where he awoke to right hemiparesis, which resolved spontaneously after few hours. His past medical history was significant for asthma and history of primary syphilis five years ago, which was treated with a single dose of penicillin G benzathine (2.4 million units intramuscularly). Prior to treatment, the serum RPR (Rapid Plasma Regain) was 1:32. After treatment, repeat RPR titre was not obtained. He has smoked one-half of a pack of cigarettes daily for ten years and denied any intravenous drug use. He admitted to unprotected sexual intercourse with men. The physical examination performed was within normal limits. The neurological examination was positive for right facial paralysis sparing the forehead with labial dysarthria, right upper extremity, and lower extremity spastic hemiparesis with a strength of 3 out of 5 on the Medical Research Council scale, and impaired fine touch, pinprick, and proprioception sensation on the right hemibody. The patient was not within the time frame for possible intravenous thrombolytic use. Routine laboratory investigations were normal except

for an elevated C-reactive protein of 12.6 mg/L. A non-contrast magnetic resonance imaging (MRI) of the brain revealed a subcortical infarct (Figure 1). A conventional cerebral angiogram did not show any evidence of vasculitis, arterio-venous malformation, stenosis, or occlusion. Transesophageal echocardiogram (TEE) did not reveal any embolic source, and routine telemetry did not reveal any arrhythmias. He underwent loop recorder implantation which did not show any subclinical episodes of atrial fibrillation on one-year follow-up. Hypercoagulable work-up was abnormal for elevated Anticardiolipin IgG (47.4 GPL) and IgM (74.1 GPL), D-Dimer, and Factor VIII Activity. Protein C activity was below normal limits. Antithrombin Activity, normal dRVVT, Anticardiolipin IgA, and free Protein S Ag were all within normal limits. ANA, Factor V Leiden Mutation, and Prothrombin gene mutation were

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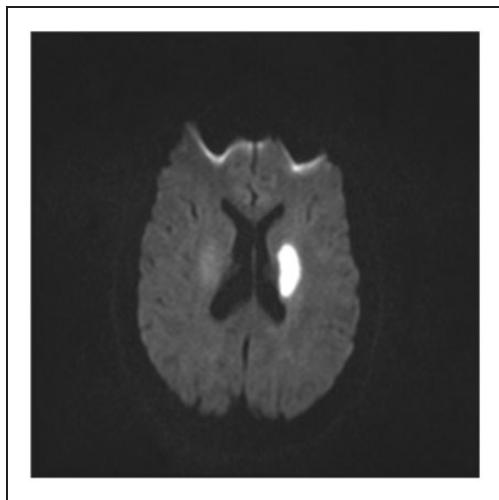


Figure 1. MRI brain showing hyperintensity in left corona radiata with restricted diffusion compatible with acute infarct.

all negative. Serum protein electrophoresis was negative for monoclonal bands. Serum RPR was reactive in 1:512 dilution, and subsequent TPPA (Treponema Pallidum Particle Agglutination) assay was also reactive. HIV (human immunodeficiency virus)-1/2 antibody immunoassay was positive for HIV-1 antibodies, and the CD4 cell count was low at 321 cells/uL. CSF (cerebrospinal fluid) analysis revealed a low glucose of 18 mg/dL, increased protein to 152 mg/dL, and pleocytosis of 35 wbc/ μ L with 85% neutrophils in tube 1 and 65 wbc/ μ L with 93% neutrophils in tube 4. CSF VDRL (Veneral Disease Research Laboratory) test was reactive to 1:32. CSF IgG was elevated to 72.2 mg/dL. CSF myelin basic protein was normal at <2.0 mcg/L. CSF oligoclonal banding showed no bands. No acid fast bacilli were seen on CSF smear. CSF cultures including bacterial, viral, AFB, and fungal were all negative. Other specific opportunistic pathogens were not tested in CSF. The patient was diagnosed of neurosyphilis superimposed on HIV and was treated with intravenous penicillin at 24 million units for ten days followed by once-weekly intramuscular penicillin injections containing 2.4 million units for the following three weeks. On follow-up with infectious disease, genotype testing for resistance patterns showed no predicted resistance. With different options available, highly active antiretroviral therapy (HAART) that included boosted protease inhibitor was preferred to allow high barrier to developing any resistance. In three months after stroke, he was started on tenofovir-emtricitabine plus darunavir-cobicisat without any complications. Due to insurance issues, cobicisat was substituted with ritonavir. After four weeks of therapy, his viral load dropped from 55,000 copies/mL prior to therapy to

740 copies/mL, and undetectable by six months. CD4 cell count improved from 321 cell/uL to 499 cells/uL. RPR titre decreased from 1:512 prior to therapy to 1:32 at six months. A repeat CSF analysis was planned; however, given his excellent clinical response and decrement in serum RPR, repeat invasive testing with lumbar puncture was not performed. Also, six months after the stroke, repeat hypercoagulable work-up showed decline in anticardiolipin IgG and IgM to 17 and 18, respectively, and normalization at one-year follow-up. D-dimer and fibrinogen were also normal.

Discussion

This case has several salient points. First is the importance of screening high-risk groups like men who have sex with men for syphilis due to higher prevalence of syphilis in these groups in post-antibiotic era.^{1,2} Traditional screening algorithms start with non-treponemal tests followed by confirmation with treponemal tests. However, recently reverse sequence screening algorithm is becoming popular where treponemal test is used for screening followed by non-treponemal tests.³ This new approach has advantages of identifying those with very early syphilis, prior treated syphilis and very late cases of syphilis as all these groups can have non-reactive non-treponemal tests but would be positive for treponemal tests. The positive predictive value of treponemal tests as screening tests is about 90% in high-risk groups.⁴ Ischemic stroke could be the only presenting symptom and inflammatory response due to syphilis could be absent due to immunocompromised states like HIV which can co-exist due to same high-risk behaviour. While several cases of neurosyphilitic ischemic stroke in HIV-positive patients have been reported, this case emphasizes importance of high-risk behaviour like men who have sex with men. Also, extensive stroke work-up was performed in this case that included hypercoagulability, TEE, and even a loop recorder implantation based on new evidence.⁵ Such extensive work-up was either negative or false positive, thus the most likely mechanism of his infarct being meningovascular syphilis. Meningovascular syphilis occurs in 10% of all cases of neurosyphilis, with peak occurrence and pathological changes on an average of seven years after primary infection.⁶ In 25% of cases, there is a prodrome of headaches and neuropsychiatric symptoms from diffuse meningoencephalitis preceding the vascular insult. The prodromal symptoms were absent in this case likely due to marked immunosuppression from the underlying HIV infection. The most common mechanism postulated for stroke in neurosyphilis is an obliterative arteritis known as Heubner arteritis. It affects large- and medium-sized vessels which can be seen

on any angiogram; however, factors like smoking could confound the results. Another form of arteritis associated with neurosyphilis is called Nissl-Alzheimer arteritis affecting smaller vessels, where even a conventional angiogram could appear normal and the pathology could be detected only on autopsy. This patient had an infarct in an area supplied by the lenticulostriate branches of middle cerebral artery. Given the small size of these vessels and normal angiogram in the patient, likely mechanism of the infarct was Nissl-Alzheimer arteritis. While lipohyalinotic small vessel disease from smoking is a possibility, the MRI did not show any evidence of chronic small vessel ischemic changes. The tests for hypercoagulability could be due to false positives in the setting of the active inflammatory processes of HIV and syphilis as repeat testing after treatment showed normalization of anticardiolipin antibodies. Another possibility is elevated anticardiolipins as potential cause of infarct; however, lupus anticoagulant activity associated with thrombosis has been reported only for people with antiphospholipid syndrome, either primarily or secondary to lupus. The second highlight of the case is the approach to syphilis when HIV coexists. If a patient has been previously treated for syphilis, a fourfold decline in non-treponemal antibody titre used to categorize between cure, relapse/reinfection, or serofast stages is based on consensus that has not been tested. This young man could have been reinfected due to continued unprotected sexual activity. Another possibility is treatment failure, which can be associated with HIV. Further, the non-treponemal antibody titre fluctuates in HIV, thought to be related to B-cell dysregulation leading to the production of anti-phospholipid antibodies. Because of this, the CDC (Centers for Disease Control and Prevention) recommends a lumbar puncture in HIV patient with CD4 cell counts below 359 cells/mL or a serum RPR titre $\geq 1:32$ as they are more likely to have CSF abnormalities consistent with neurosyphilis.⁷ A positive CSF VDRL has low sensitivity but high specificity in the absence of blood contamination. CSF treponemal tests (particularly fluorescent treponemal antibody absorption [FTA-ABS]) have high sensitivity but low specificity. Thus, CSF should be tested for both VDRL and FTA-ABS. CSF RPR has a high false-negative rate.⁸ This patient also had low glucose in CSF. The patient was nil per os for more than 12 h with serum glucose of 60 mg/dL. Low glucose was likely secondary to low serum glucose since CSF cultures for bacteria, tuberculosis, and fungus were negative. Additionally, HIV is associated with CSF pleocytosis, so the CDC recommends the cut off of cell count in CSF to be at 20 for neurosyphilis if the patient is HIV-positive and not on HAART. This patient was treated as per current CDC guidelines.⁹

No randomized controlled trials have tested the route of administration and duration of the recommended regimen for neurosyphilis. Since duration of intravenous regimen is shorter than the duration of the regimen used for latent syphilis, weekly intramuscular therapy for three weeks is recommended after completion of intravenous therapy. Evidence suggests that despite aggressive or enhanced treatment, HIV patients with neurosyphilis are more likely to fail therapy¹⁰ both clinically and serologically leading to relapses or long-term sequelae. However, their outcome can be improved by HAART.¹¹ This was observed in our case. The patient showed good serological response and did not have any new neurological symptoms. Even if remission occurs, men who have sex with men are at high risk of reinfection. CDC recommends repeat CSF examination in six months for resolution of pleocytosis since improvement in CSF protein and CSF antibody titre lags behind normalization of CSF pleocytosis. In this case, repeat CSF analysis was deferred due to excellent clinical response and normalization of serum RPR titre. Evidence suggests that normalization of serum RPR can predict treatment success in patients with neurosyphilis who also have HIV receiving HAART as compared to those not receiving antiretroviral therapy.¹² In summary, stroke in young patients warrants testing for syphilis, especially in men who have sex with men since they are more likely to have asymptomatic meningo-vascular neurosyphilis. The use of current CDC recommendations for diagnosis of neurosyphilis is a reliable evidence-based practice; however, treatment is based on consensus rather than robust data. Prognosis is poor in syphilis associated with HIV, but HAART can improve the outcome.

Declaration of conflicting interests

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Informed consent

An informed verbal consent was obtained from the patient by Dr Wang.

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