

# Neurosypilis: mighty imitator forays with benign presentation and unique neuroimaging findings

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**Abstract.** **Background:** Common causes of temporal lobe hyper intensities are central nervous system infections like herpes simplex encephalitis, Lyme disease, limbic encephalitis and vascular pathology like Cerebral Autosomal Dominant Arteriopathy with Subcortical infarcts and Leukoencephalopathy. **Methods:** Personal assessment, laboratory data analysis and neuroimaging for the patient who was admitted to a central Pennsylvania tertiary care referral centre were conducted. **Results:** A 52-year-old male presented with a 1-year history of diffuse dysesthesia in upper and lower extremities with associated intermittent headaches and neck stiffness. Evaluation with lumbar puncture revealed increased nucleated cells (50 ul) with lymphocytic predominance (96%) and an elevated protein level of 109 mg/dl. Magnetic resonance imaging (MRI) of the brain showed T2/FLAIR hyper intensity in bilateral subcortical temporal white matter, left-greater-than-right and associated volume loss in cerebral parenchyma. Additional abnormal work up included reactive serum reactive plasma regain and *Treponema pallidum* antibody particle agglutination. Diagnosis of neurosyphilis was made and the patient was treated with intramuscular (IM) penicillin for 3 weeks. At the time of discharge, his headache and neck stiffness resolved and dysesthesias were decreased in intensity. **Conclusions:** The diagnosis of neurosyphilis is intricate, and no reference standard exists. Neuroimaging findings of neurosyphilis commonly are cerebral infarctions, leptomeningeal enhancement or non-specific white matter lesions. Less common features on fluid-attenuated inversion recovery (FLAIR) sequences are cortical atrophy and mesial temporal parenchymal signal changes. It is prudent to keep neurosyphilis in differential of mesial temporal lobe white matter changes, as early diagnosis and treatment results in better prognosis.

**Additional keywords:** Mesial temporal white matter changes, Neurosyphilis, IM Penicillin.

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## Introduction

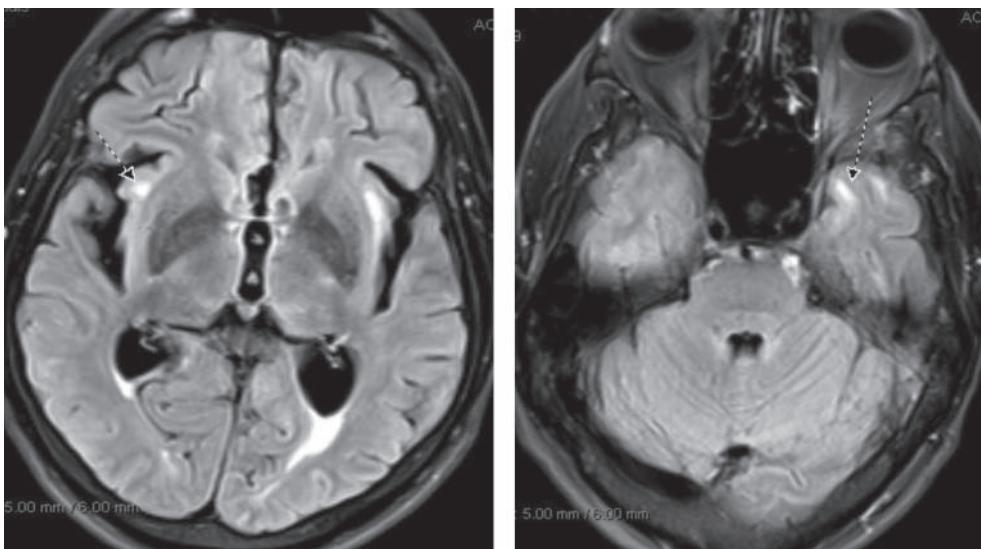
Neurosypilis occurs by the invasion of spirochete *Treponema pallidum* into the cerebrospinal fluid (CSF). The clinical presentation can range from transient meningitis to cognitive disorders and, in some instances, movement disorders as well. Neuroimaging in the diagnosis of neurosyphilis can yield unique findings and is diagnostically rewarding due to the complexity of the diagnostic process, which is linked with false-negative test results.

## Case report

A 52-year-old, hitherto healthy, Latin-American male presented for the first time to an outpatient neurology clinic with a 1-year history of diffuse dysesthesia involving the upper and lower extremities, with intermittent headaches and neck stiffness. His headaches were characterised as holocephalic, throbbing in quality, moderate in severity, and lasting for a couple of hours per day. There was no associated auras or photophobia. Dysesthesias were described as burning pain with tingling sensation, radiating from the back of his head down to his

neck and to all four extremities. His symptoms manifested almost daily, but were exacerbated upon lifting heavy objects or bending over. The patient was placed on gabapentin and nortriptyline by his general practitioner (GP), but his symptoms continued to worsen, so he was referred to a neurologist for further evaluation. The patient's past medical and family histories were unremarkable, but his social history was notable for multiple sexual partners. His neurological examination (mental status, cranial nerves, motor, sensory, coordination and gait) was also unremarkable.

The patient underwent electrodiagnostic testing, which revealed no evidence of a radiculopathy, plexopathy or large fibre polyneuropathy affecting either extremity. A Lumbar spine MRI showed moderate-to-severe neural foramina stenosis right L4-L5 and bilateral L5-S1. A brain MRI (Fig. 1) showed T2/FLAIR hyper intensity in bilateral subcortical temporal white matter, left-greater-than-right and associated volume loss in cerebral parenchyma. Based on the brain MRI findings, an electroencephalogram (EEG) was conducted, which showed no evidence of focal slowing or epileptiform activity. Routine blood



**Fig. 1.** Brain MRI axial images: fluid attenuation inversion recovery shows hyper intensity in bilateral subcortical temporal white matter.

tests including a comprehensive metabolic panel, liver function and thyroid test were normal. Human immunodeficiency virus (HIV) 1 and 2 antibodies were negative. Cerebrospinal fluid testing revealed increased nucleated cells (50  $\mu$ L) with lymphocytic predominance (96%) and an elevated protein level of 109 mg/dL. Lyme disease serology and polymerase chain reaction (PCR) in serum and CSF were negative. Herpes simplex virus PCR was negative both in CSF and blood, but the reactive plasma reagin test (RPR) was highly positive at 1:128 in serum, and *Treponema pallidum* antibody particle agglutination was reactive as well. The venereal disease research laboratory (VDRL) test for CSF was conducted and was negative.

Based on clinical presentation, laboratory data and neuroimaging findings, a diagnosis of neurosyphilis was made and the patient was treated with intramuscular penicillin G for a duration of 3 weeks.<sup>1</sup> Upon follow up after 4 weeks, the patient's condition clinically improved as his headaches and neck stiffness resolved and dysesthesias were decreased in intensity. The patient refused repeat testing, including lumbar puncture or MRI.

## Discussion

Syphilis is a chronic infection caused by *Treponema pallidum*. Syphilis progresses through four stages if untreated; primary, secondary, latent and tertiary stages. Neurosyphilis is further classified as early and late syphilis, with meninges and vascular phenomenon occurring in early, and brain tissue getting affected in late, neurosyphilis.<sup>2</sup>

Neurosyphilis creates confusion in the clinical world due to its multifaceted presentation and lack of sensitivity to diagnostic testing.<sup>3</sup> This disease has a huge variety of presentations, with clinical manifestations ranging from asymptomatic neurosyphilis, meningo-vascular syphilis, to florid meningitis. The diagnosis of neurosyphilis is intricate and no reference standard exists, but an algorithm is usually followed. Thus, diagnosis requires

serologic confirmation of syphilis infection (any stage) with both non-Treponemal (NTT) and Treponemal tests (TT), followed by CSF-VDRL testing. The CSF-VDRL test is the standard test for neurosyphilis; however, despite its very high specificity (99.8%), its sensitivity is only 50%.<sup>4</sup> As a result, clinicians also rely on indirect markers of central nervous system (CNS) inflammation such as an elevated white blood cell (WBC) count or protein in the CSF.<sup>5</sup> In serum-positive syphilis patients, the CSF nucleated cell count of  $5 \times 10^6$  E6/L and greater is regarded as cut-off for treatment initiation due to the poor sensitivity of the CSF-VDRL test.<sup>6</sup> In contrast, patients who are serologically negative for syphilis, but have a positive CSF-VDRL test result, are unlikely to have neurosyphilis.<sup>7</sup> Therefore, treatment decision needs to be weighed carefully. The patient described above had positive serology for both TT and NTT, with elevated CSF nucleated cell count ( $>5 \times 10^6$  E6/L) and protein, but a negative CSF-VDRL test.

Due to the above limitations, additional support to help with diagnosis, such as neuroimaging (e.g. MRI), is beneficial. Brain MRI findings for neurosyphilis are non-specific, and no radiologic or pathognomonic findings have been reported to date. Infrequently, it can present on fluid-attenuated inversion recovery (FLAIR) sequences as cortical atrophy and mesial temporal parenchymal signal changes. It has also earned the reputation of an imitator of herpes simplex or limbic encephalitis because of its the mesial temporal changes involved. More common neuroimaging findings for neurosyphilis are cerebral infarctions, leptomeningeal enhancement or non-specific white matter lesions.<sup>8</sup> Our patient had both mild atrophy and temporal changes on MRI.

Neurosyphilis is generally not considered high in differential of temporal lobe hyper intensities; common causes usually are nervous system infections like herpes simplex encephalitis, Lyme disease, limbic encephalitis and vascular pathology like Cerebral Autosomal Dominant Arteriopathy with Subcortical infarcts and Leukoencephalopathy (CADASIL).<sup>9</sup> Subtle temporal

atrophy helps differentiate out neurosyphilis; while Herpes simplex encephalitis is characterised by a mild mass effect with profound cortical and subcortical oedema.<sup>10</sup> Herpes simplex virus (HSV) encephalitis is commonly encountered as acute monophasic disease, and it is rare for a chronic infection can be encountered, which can further progress into chronic granulomatous encephalitis.<sup>11</sup> In CADASIL, common findings are white matter changes at anterior temporal lobes.<sup>12</sup> Our patient had no clinical correlate-like cognition deficits or weakness. Lyme disease was considered, but meningeal and nerve enhancement is relatively common and in addition to positive titres in serum.<sup>13</sup> Limbic encephalitis was ruled out because the patient had normal cognition and paraneoplastic testing was negative.

Despite the current era of medical advancement, the incidence of syphilis is increasing, and cases are being encountered in developed countries as well. As neurosyphilis mimics so many diseases, it is pertinent to be aware of its presentation in this era of HIV–AIDS.<sup>9</sup> This differential should be considered in HIV-negative patients as well. It is also important to consider a patient's social history as our patient tested negative for HIV. Our patient experienced a delay in diagnosis because, despite worsening symptoms and not responding to conventional treatment for his headaches, no further testing was prescribed by the GP. When this patient presented to neurology, an MRI was conducted and broad differentials were considered; tests specific to syphilis were ordered, which led to the ultimate diagnosis and successful treatment of the disease.

Thus, it is prudent to keep neurosyphilis in differential of mesial temporal lobe white matter changes as early diagnosis and treatment results in better prognosis. Treatment of neurosyphilis is carried out using penicillin; no resistance to penicillin has been reported and the patient outcome is quite good if treatment commences early after diagnosis.

### Conflicts of interest

The authors declare no conflicts of interest.

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