Limbic Encephalitis Caused By Neurospyhilis in a HIV-Positive Male: Case Report and Review

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Abstract

Neurosyphilis can present with a wide range of different presentations. For this reason, it has been called the “the great imitator”. Limbic encephalitis mimicking HSV encephalitis is an under recognized manifestation of neurosyphilis. Co-infection with HIV may alter the course of neurosyphilis and cause more atypical and aggressive presentations to occur. The author presents a case of mesial temporal encephalitis caused by neurosyphilis in a man with concomitant HIV infection. A review of the literature shows that this is not a sparse presentation of neurosyphilis. The pathophysiology and clinical implications are reviewed.

Keywords: Syphilis; Neurosyphilis; Encephalitis; HIV; PLEDs; Mesial temporal lobe; Limbic; Amnesia

Introduction

Case

A 51-year-old man presented with a 3-week history of personality changes, progressive amnesia, and bitemporal headaches. On admission, his vital signs and general physical examination were normal. However, he appeared to be experiencing delusions and visual hallucinations. His short term memory was severely impaired and he required frequent reorientation. He confabulated and claimed to have known each of the medical staff at one point in his life. His speech was otherwise fluent and he was able to follow 3-step complex commands. Neurological exam showed impairments in recall, visuospatial, and executive functions. The rest of his examination was normal.

Brain MRI showed increased T2 signal within the bilateral frontal and mesial temporal lobes suspicious for encephalitis (Figure 1a). A lumbar puncture (LP) revealed a cerebrospinal fluid (CSF) glucose of 48 mg/dL, erythrocytes 3/mL, leukocytes 220/mL (lymphocytes 69%, neutrophils 11%, monocytes 20%), and CSF protein of 205 mg/dL. He was started empirically on intravenous acyclovir. CSF analysis for herpes simplex virus (HSV), West Nile virus, and other infectious testing were negative. Malignancy workup including CSF cytology and paraneoplastic antibodies was also negative.

The patient’s wife noted that he was recently engaged in promiscuous sexual behavior. Further testing for syphilis was positive as evidenced by reactive serum rapid plasma reagent (RPR) titer of 1:64, serum and CSF treponema pallidium haemagglutination assay (TPHA) titers were 1:5120 and 1:640, respectively. CSF Venereal Disease Research Laboratory (VDRL) titer was 1:16. The fluorescent treponemal antibody-absorption (FTA-ABS) test also came back positive. Acyclovir was discontinued and he was started on a 21 day course of penicillin G. Further serologic workup revealed that he was HIV-positive with a viral load of 5140 copies and a CD4-lymphocyte count of 396. The CD4 percent was 24% and the CD4/CD8 ratio was 0.6.

Figure 1a: Brain MRI without contrast: Abnormal T2 and FLAIR signal abnormalities and atrophy within the bilateral frontal and mesial temporal lobes (arrows).

His hospital stay was complicated by recurrent generalized tonic-clonic seizures requiring intubation and treatment with Fosphenytoin. Electroencephalogram (EEG) showed independent bitemporal periodic lateralized epileptiform discharges (PLEDs). He was successfully extubated and a repeat LP performed ten days into the course of antibiotic therapy showed marked decrease in the amount of CSF protein (80 mg/dL) and leukocytosis (34/mL).

Prior to his hospital discharge, he was started on highly active antiretroviral therapy with tenofovir, efavirenz, and emtricitabine. Six weeks later during outpatient follow-up, he was able to hold a complex conversation. However, he continued to demonstrate severe short-term memory and confabulated about activities he had done earlier in the day and what he had for breakfast. Repeat MRI of the brain showed improvement of the T2 and FLAIR signal abnormality within...
the frontal and mesial temporal lobes (Figure 1b). However, there was progression of atrophy of the mesial temporal lobes suggesting irreversible damage. At 6 months follow-up, the patient had a repeat LP that showed no pleocytosis, CSF-protein of 42 mg/dL, and CSF-VDRL was nonreactive. The CD4 count had increased from 396 to 625 and CD4 percent increased from 24% to 42%. The HIV viral load was undetectable.

Discussion

Neurosyphilis refers to infection of the central nervous system (CNS) by the spirochete Treponema pallidum. This may occur anytime within weeks of the initial inoculation to years during the late stage of tertiary syphilis. If it occurs acutely, it may be latent and asymptomatic or may present as meningitis, strokes, vertigo, optic neuritis, uveitis, or more rarely as basilar meningitis with cranial neuropathies. The pathophysiology involves an acute meningoovascular and ocular inflammation caused by small vessel arteritis [1-3].

More commonly, neurosyphilis occurs many years later in the tertiary stage of syphilis manifested by general paresis and tabes dorsalis. In general paresis, chronic infection of the brain parenchyma causes widespread parenchymal damage leading to forgetfulness and personality changes [1]. Tabes dorsalis is caused by demyelination of the posterior columns, dorsal roots, and dorsal root ganglia leading to impaired proprioception and gait imbalance.

Due to its frequent atypical presentations, syphilis has been commonly called "the great imitator". The case presented describes neurosyphilis mimicking herpes simplex virus (HSV) encephalitis. The subacute presentation of altered mental status, bilateral mesiotemporal T2 hyperintensity on MR images, and temporal PLEDs on EEG have always been thought of as pathognomonic signs for herpes encephalitis. Other uncommon and rare entities have been reported to have similar imaging findings including paraneoplastic limbic encephalopathy, lupus erythematosus, Hurst hemorrhagic leukoencephalopathy, and gliomatosis cerebri [4]. An extensive review of the literature demonstrates 29 cases worldwide with mesial temporal lobe encephalitis as a rare manifestation of neurosyphilis [4–26] (Table 1). All the patients presented similarly with confusion, memory disturbance, or change in personality. Scheid et al. and other authors listed in Table 1 recommend including neurosyphilis in the differential diagnosis of limbic encephalitis [25].

Case Year Patient Age/sex Symptoms before diagnosis Labs and HIV status MRI Findings Clinician and or MRI Follow up

Bash et al. [4] 2001 50 M 3 months CSF cells : 19 WBC/uL, (93% lymphocytes) CSF Glucose 45 mg/dL CSF protein 87 mg/dL Serum RPR titer 1:64 MHA-TP: Positive CSF -VDRL titer 1:16 FTA-ABS: Positive HIV: UK Cortical and subcortical increased T2-FLAIR signal in the bilateral mesial temporal region. There was also mild bilateral temporal lobe atrophy. Four months later, the patient had significant cognitive and radiographic improvement. MRI showed improvement in the previously noted mesial temporal FLAIR and T2 lesions.

Elisa et al. [5] 2011 43 M 1 week CSF cells: 26.4 WBC/uL, (mostly lymphocytes) CSF protein 92.9 mg/dL Serum RPR titer 1:256 Serum TPHA titer 1:20480 CSF-TPHA titer 1:10240 CSF-VDRL titer 1:32 HIV ½ Ab: Negative Asymmetrical bilateral cortical and subcortical increased T2-FLAIR signal in the mesiotemporal region and insula. Atrophy involving the bilateral mesiotemporal region. 2 weeks after treatment, repeat brain MRI showed extension the T2- FLAIR hyperintensities in the left mesiotemporal region and insula.

Denays et al. [6] 1999 51 F Acute CSF cells: 23 WBC/uL (80% lymphocytes). CSF protein 46 mg/dL CSF glucose: normal Bilateral mesiotemporal lesions, predominantly on the left side Prior to discharge, there was a marked improvement of memory and regression of MRI lesions. She was able to return to work.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Symptom(s)</th>
<th>Test Results</th>
<th>Imaging Findings</th>
<th>Clinical Outcome</th>
</tr>
</thead>
</table>
| Angus et al. [7] | 1998 | 34 M | UK | UK | PHA titer 1:40960  
FTA-ABS titer 1:12800  
HIV: UK | High signal in the left temporal lobe on T2- FLAIR sequences and white matter abnormalities. | Within 1 week of therapy, the patient was oriented and could hold a complex conversation, although short-term memory deficits remained. |
| Szilak [8] | 2001 | 55 M | UK | Acute | CSF cells: 79 WBC/uL  
(93% lymphocytes)  
CSF protein 71 mg/dL  
CSF glucose 65 mg/dL.  
Serum treponemal IgG titer 1 : 64  
(Confirmed by microhemagglutination assay).  
HIV ½ Ab: Negative | Increased signal in the temporal lobes, amygdala, hippocampus, and insula. | Three months later, the patient had improved cognitive function. A repeat MRI showed marked improvement in the previously identified bilateral hyperintensities, with residual atrophy. |
| Bousende et al. [9] | 2012 | 43 M and 45 M | UK | UK | Lab results were noted to be compatible with neurosyphilis (TPHA and VDRL) HIV: UK | | |
| Omer et al. [10] | 2012 | 55 M | 6 months | CSF cells: 16 WBC/uL  
(100 percent mononuclear cells)  
CSF protein 77mg/dL  
CSF glucose was normal  
Gram stain was negative.  
Serum and CSF were noted to have positive TPHA. HIV serology was negative. | High T2 signal intensity and atrophy of the right frontal and bilateral mesial temporal areas. | | |
| Fadil et al. [11] | 2006 | UK | UK | UK, noted to have active syphilitic infection | Compatible with mesial temporal sclerosis. | | |
| Agayeva et al. [12] | 2013 | 51 M | 4 months | Treponemal antibody tests were noted to be positive in serum and CSF. HIV: UK | Hyperintensity of bilateral mesial temporal structures, insula, and thalami with restricted diffusion. | Six months later, there was improvement in behavior and memory. |
| Jeong et al. [14] | 2008 | 35 M | 1 month | CSF cells: 48 WBCs/uL  
(92% lymphocytes)  
CSF protein 88 mg/dL  
Gram stain negative.  
CSF-VDRL titer 1:8  
FTA-ABS: positive  
HIV: UK | High signal changes in the bilateral mesial temporal lobes including both hippocampi and amygdalae on T2- FLAIR sequences. | One month later, noted to have improved cognitive function. |
| Hama et al. [15] | 2008 | 51 M | 12 months | CSF cells: 21 WBCs/uL  
CSF protein 55 mg/dL  
CSF glucose 67 mg/dL  
Serum TPHA : 80,220 U/mL  
FTA-ABS: positive  
CSF-TPHA: 4,332 U/mL  
HIV ½ Ab: Negative | Cortical and subcortical high T2-FLAIR signal intensity areas in both mesial temporal regions and the right frontal lobe. | 2 months later, there was improved but residual cognitive dysfunction and MRI showed regression of the abnormal signal intensity in the temporal lobes. |
| Chen et al. [16] | 2005 | 52 M | 9 months | CSF cells: 8 WBCs/uL  
CSF protein 60 mg/dL  
CSFGlucose 67 mg/dL | High intensity lesions in bilateral mesial | 2 weeks after treatment, the patient became orientated but still had short-term memory impairment. |
<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Age</th>
<th>Time</th>
<th>Findings</th>
<th>Treatment/Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santos et al. [17]</td>
<td>2005</td>
<td>73 M</td>
<td>10 days</td>
<td>Serum TPHA titer 1:20480, RPR titer 1: 64, CSF-VDRL: positive HIV: UK</td>
<td>temporal regions and cortical atrophy without post-contrast enhancement. Two months later, a follow-up MRI was greatly improved.</td>
</tr>
<tr>
<td>Marano et al. [18]</td>
<td>2004</td>
<td>48 M</td>
<td>9 hours</td>
<td>CSF: 14 WBCs/uL, (94% monocytes) CSF protein 89 mg/dL CSF glucose 64 mg/dL Serum TPHA: positive CSF-VDRL titer 1:160 HIV: UK</td>
<td>Increased T2-FLAIR cortical and subcortical hyperintensities in the right mesial temporal region, cingulated gyrus, septum, and insula.</td>
</tr>
<tr>
<td>Yao et al. [20]</td>
<td>2010</td>
<td>42 M</td>
<td>9 months</td>
<td>CSF cells: 38 WBCs/uL (lymphocytes 70%) CSF protein 80 mg/dL CSF glucose was normal Gram stain was negative Syphilis TRUST titer 1:64 Serum TPHA: positive HIV serology was negative.</td>
<td>Cerebral edema and hyperintensities involving the right parietal, occipital and temporal lobes. 1-year follow-up, the patient was deemed normal in terms of neurological examination. MRI showed that the hyperintensity had disappeared.</td>
</tr>
<tr>
<td>Saunderson [21]</td>
<td>2012</td>
<td>UK</td>
<td>UK</td>
<td>UK</td>
<td>Reported to have mesial temporal changes.</td>
</tr>
<tr>
<td>Xiang et al. [22]</td>
<td>2013</td>
<td>43 M</td>
<td>5 days</td>
<td>All 6 were tested positive for TPHA, RPR, and antibodies against syphilis in the serum and CSF. HIV: UK</td>
<td>MRI in all the cases revealed T2-FLAIR hyperintensities of the unilateral or bilateral mesial temporal lobes, including the hippocampi. Patient prognoses were good in 4 that received early anti-syphilis treatment, but 2 that received delayed treatment due to misdiagnoses did not see substantial symptomatic improvements.</td>
</tr>
<tr>
<td>Derouich [23]</td>
<td>2013</td>
<td>50 M</td>
<td>UK</td>
<td>UK</td>
<td>Mesial temporal changes on MRI</td>
</tr>
<tr>
<td>Hagiwara [24]</td>
<td>2014</td>
<td>48 M</td>
<td>UK</td>
<td>Serum HIV serology was negative.</td>
<td></td>
</tr>
</tbody>
</table>
In addition to serum and CSF laboratory testing, imaging features may help to differentiate between this rare presentation of neurosyphilis and the more common HSV encephalitis. Neurosyphilis may be associated more with atrophy of the medial temporal lobe. On the other hand, gyral enhancement, cortical and subcortical edema, hemorrhage, or areas of restricted diffusion are frequently described in HSV infection [5].

It is unknown what causes the T2 hyperintensity changes in the mesial temporal lobes of patients with this atypical form of neurosyphilis. It is thought that small-vessel ischemic changes and marked meningovascular inflammation cause vasogenic, cytotoxic, and interstitial edema to occur causing parenchymal damage [4]. Another opinion is that abnormal signals are probably related to proliferation of glial cells rather than cytotoxic edema (Wang X). Coinciding seizures may also play a role in causing signal changes of the mesial temporal lobes [25]. In a study examining brain MRI abnormalities in 15 patients with general paresis, abnormal high T2-FLAIR signals were found in nine cases, mainly in the bilateral temporal, insular, and frontal lobes and hippocampus accompanied by cerebral and/or hippocampal atrophy [27]. It is yet to be determined whether mesial temporal encephalitis is part of general paresis or its own distinct manifestation of neurosyphilis.

It is unlikely that the HIV co-infection was an innocent bystander in the case described. The association between syphilis and HIV increases the risk of mesial temporal encephalitis in patients with neurosyphilis. Neurosyphilis should be considered in the differential diagnosis of any patient with HIV [31]. It has been reported that the incidence of symptomatc neurosyphilis among HIV positive individuals with early syphilis was found to be 3–4 times higher (2.1% vs 0.6%) as compared with HIV-negative persons [32]. In another study, the incidence of neurosyphilis was shown to be 23.5% in HIV-positive patients with untreated syphilis as compared to 10% in HIV-negative patients with untreated syphilis [28].

More so, in HIV positive patients, neurosyphilis may progress in an aggressive and often atypical manner [1,28,29]. It is believed that co-infection with HIV may have potentiating effects on the syphilitic infection [28,29,33]. A more fulminant form of parenchymal disease, referred to as necrotizing neurosyphilis, has also been reported to occur in patients with HIV [34]. None of the cases reports listed in Table 1 were documented as being associated with a concomitant HIV infection. This is the first reported case of neurosyphilis limbic encephalitis in a patient with HIV. It is unknown whether HIV increases the risk of mesial temporal encephalitis in patients with neurosyphilis.

It is important to note that HIV positive patients with neurosyphilis are at least 2.5 times less likely to normalize the CSF-VDRL reactivity after penicillin treatment. This risk is even higher if the CD4+ T-cell count is <200 cells/µL [35]. Thus, the Centers for Disease Control and Prevention treatment guidelines recommend that HIV positive patients with neurosyphilis undergo routine CSF examination every 3–6 months until the cell count normalizes [33,36].

Prognosis of limbic encephalitis due to neurosyphilis varies. Among the 18 patients listed in Table 1 with follow-up data, 11 showed mild to moderate clinical and or radiographical improvement following antibiotic therapy, 1 required retreatment for recurrent relapses, and 6

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Table 1: M: male; F: female; CSF: cerebrospinal fluid; UK: data unknown or unavailable; WBC: white blood cell; VDRL: Venereal Disease Research Laboratory; RPR: Rapid plasma reagin; TPHA: Treponema pallidum haemagglutination assay; microhemagglutination assay for Treponema pallidum antibodies (MHA-TP); FTA-ABS: fluorescent treponemal antibody-absorption; TRUST: Toluindine Red Untreated Serum Test.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Sex</th>
<th>Age</th>
<th>Follow-up</th>
<th>CSF Cells</th>
<th>CSF Protein</th>
<th>CSF VDRL Titer</th>
<th>CSF-TPHA Titer</th>
<th>Serum VDRL Titer</th>
<th>Serum RPR Titer</th>
<th>Gram Stain</th>
<th>CSF Glucose</th>
<th>CSF WBCs/uL</th>
<th>MRI Findings</th>
<th>Laboratory Findings</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lessig et al. [26]</td>
<td>2006</td>
<td>57 M</td>
<td>4 months</td>
<td></td>
<td>CSF cells 22 WBCs/uL</td>
<td>CSF protein 157 mg/dL</td>
<td>CSF glucose 44 mg/dL</td>
<td>Serum VDRL titer 1:8</td>
<td>Serum TPHA titer 1:81920</td>
<td>CSF-TPHA titer 1:524288</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bilateral FLAIR hyperintensities in the temporal lobes and frontal tips with gadolinium enhancement, and diffuse atrophy.</td>
<td>Repeat MRI showed atrophy of left medial temporal lobe.</td>
</tr>
</tbody>
</table>

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Scheid [25] 2005 34 M UK CSF cells 22 WBCs/uL CSF protein 95 mg/dL Serum VDRL titer 1:8 Serum-VDRL titer 1:4 Serum TPHA titer 1:81920 CSF-TPHA titer 1:524288. HIV % Ab: negative. T2-FLAIR hyperintense signal alteration in the left medial temporal lobe. After 8 months, there was still cognitive slowing and impaired a memory. Repeat MRI showed atrophy of left medial temporal lobe. |

Table 1: M: male; F: female; CSF: cerebrospinal fluid; UK: data unknown or unavailable; WBC: white blood cell; VDRL: Venereal Disease Research Laboratory; RPR: Rapid plasma reagin; TPHA: Treponema pallidum haemagglutination assay; microhemagglutination assay for Treponema pallidum antibodies (MHA-TP); FTA-ABS: fluorescent treponemal antibody-absorption; TRUST: Toluindine Red Untreated Serum Test.
had no improvement or worsening of their disease. Early diagnosis and treatment has been shown to improve outcome [22].

Conclusion

Neurosyphilis continues to surprise us with atypical and new presentations. A review of the literature argues that it should be considered in the initial diagnostic workup of limbic encephalitis and not just a mere diagnosis of exclusion. Concomitant HIV infection is common and may change the presentation of neurosyphilis. Clinicians need to be aware of the different manifestations so that early treatment can potentially decrease morbidity in this subgroup of patients.

References