Neurosyphilis-Induced Psychosis

The return of the great imitator makes it critical to know the guidelines for testing for neurosyphilis.

By Veronica Hocker, MD and Nabil Ali, MD

Epidemiology
In the early 20th century, new-onset psychosis secondary to neurosyphilis was common. With the advent of antibiotics, cases of neurosyphilis-induced psychosis became rare. A rise occurred in the late 20th century with the rise of HIV coinfection. Today, sexually transmitted infections are increasing in the US. The Centers for Disease Control and Prevention (CDC) stated in August 2018 that diagnoses of syphilis increased 76% from 2013 to 2017, which may be understated as many cases are not diagnosed. In a CDC report in 2016, rates of primary and secondary syphilis increased from 2.1 (2000-2001) to 8.7 (2015–2016) cases per 100,000.

It would not be surprising in this context if neurosyphilis was also increasing. However, the clinical suspicion for neurosyphilis is as low as 36%, delaying diagnosis and treatment by as much as 24 months. For clinical neuropsychiatrists, syphilis testing is among the standard laboratory tests obtained during admission or changes in behavior or cognition.

Natural History
Syphilis is treatable and, when treated in the early stages, should not progress to neurosyphilis. With antibiotics, there is less disease progression, which may explain the low clinical suspicion. Neurosyphilis can occur at any stage of infection and take many different forms, from seemingly benign meningitis, to meningovascular disease leading to strokes, to tabes dorsalis, or general paresis. This has earned neurosyphilis the epithet of “the great imitator.” Although more severe manifestations typically occur 10 to 25 years postinfection, psychosis and general paresis can occur as early as 2 years postinfection; in the prepenicillin era, it was described at 8 months postinfection.

Case Studies
We discuss 2 patients with different presentations in order to discuss testing considerations and to demonstrate the importance of carefully considering syphilis in presentations of cognitive decline, psychosis, and catatonia (Case 1 and Case 2).

Discussion
Both patients had partially treated syphilis and no history of psychotic illness or cognitive disorder. Per collateral reports, the patients did not have a family history of mental illness. Both were outside of the usual age for a first break psychosis. It is now clear that the history of the patient in Case 1 had a gradual progression of suspicious symptoms. It could be argued that the patient in Case 2 may have also showed symptoms prior to the psychosis. The cerebrovascular accident that occurred in his 40s could have been a product of meningovascular complications of neurosyphilis. The diagnoses of hypertension and diabetes, also increasing his risk of stroke, overshadowed consideration of syphilis as an underlying cause.

These cases emphasize the importance of testing for syphilis in new-onset psychotic and cognitive disorders, as well as ensuring complete treatment to prevent further complications and disability. The algorithm for testing varies depending on the institution, starting with either nontreponemal testing followed by treponemal testing or vice versa (Table).

Careful review of a patient’s clinical history is required to guide testing and treatment for syphilis.

High suspicion for neurosyphilis led to cerebrospinal fluid (CSF) analysis in both cases, allowing for appropriate diagnosis and treatment. It is notable that the patient in Case 2 had a negative CSF venereal disease research laboratory (VDRL) test. Considering only CSF VDRL, he may not have received treatment specifically for neurosyphilis. With appropriate treatment, both cases showed great clinical improvement. Antipsychotics were no longer needed for (Continued on page 78)
Case 1. A Man Treated for Psychosis

History
A man, age 36, with no psychiatric history other than cannabis use disorder in remission for 2 years had medical history notable for a positive rapid plasma reagin (RPR) titer 8 years earlier without documented treatment. Per collateral account, 1 year ago he started having increased clumsiness with slowed movements, increased forgetfulness, and soft, stuttering speech. Approximately 6 months later, he had forensic medical evaluation after breaking and entering. At that time, his RPR titer was 1:500. He received partial treatment. During the next few months, he had multiple hospitalizations for disorientation, psychosis (paranoia and hallucinations), and catatonia. He had multiple trials of high-dose antipsychotics with no response. In medical records, he was noted to be mute, not eating, not drinking, and standing still for long periods of time in odd positions.

Clinical Presentation
At the time of presentation, the patient continued to be combative but also had long stretches of posturing at the edge of his bed. His vital signs fluctuated dramatically. He was started on lorazepam, with no response other than stabilization of vital signs. Although he received a total daily dose of 22 mg lorazepam for catatonia, he had a Bush-Francis Catatonia Rating Scale (BFCRS) score of 28, notable for mutism, negativism, stereotypy, psychomotor persistence, grasp reflexes, catalepsy, echopraxia, and perseveration. Neurologic examination was limited by combative ness but was notable for bradyphrenia, bradykinesia, and diffuse hyperreflexia. Follow-up examination during periods of improved cooperation additionally revealed decreased visual acuity, dysarthria, left-sided weakness, decreased vibratory sensation to the knees, left greater than right hyperreflexia, and dysmetria.

Laboratory Testing
Findings from the patient’s laboratory studies were notable for a creatinine kinase level of 815, negative HIV-screen, negative urine drug screen (UDS), reactive T. pallidum, and an RPR titer of 1:32. Subsequent cerebrospinal fluid (CSF) analysis revealed a venereal disease research laboratory (VDRL) of 1:64 without pleocytosis. Brain MRI with and without contrast showed global cerebral atrophy with ventriculomegaly (including the temporal horns and third ventricle) (Figure). EEG demonstrated diffuse beta activity with no epileptiform activity.

Treatment
Given the history of partial treatment for syphilis, clinical examination findings, and positive CSF VDRL, the patient was treated for neurosyphilis with IV penicillin G. For the catatonia secondary to neurosyphilis, he was continued on lorazepam, started on electroconvulsive therapy 3 times per week, and started on memantine and zolpidem. With treatment, his clinical picture greatly improved. He had improved alertness, responsiveness, speech, reality testing, and ambulation. He was able to play chess (frequently defeating medical students) and make artwork. He continued to have bradykinesia, hypertonicity (improved), left upper extremity flexor posturing with spasticity, hyperreflexia, intention tremor, and distal weakness.

Follow-Up
The patient was eventually discharged home with a BFCRS score of 0 and no evidence of psychosis; however, he had residual difficulties with executive function and memory as well as a slowed gait and residual weakness in his left arm. His discharge medications were lorazepam 1 mg twice a day and zolpidem 10 mg at night for sleep. Repeat CSF analysis 6 months after presentation showed an appropriate decline in VDRL titer to 1:8. Repeat outpatient testing was scheduled for another 6 months later.

Figure. Brain MRI without contrast showing global cerebral atrophy and widening of ventricles (temporal horns, 3rd ventricle).
Case 2. A Man With Prefrontal and Mesiotemporal Cognitive Deficits

History

A man, age 59, with a silent stroke that occurred in his 40s and history of hypertension and type 2 diabetes, had no prior psychiatric history other than alcohol and cocaine use disorder. He exhibited bizarre behaviors (defecating on trays), disorganized and tangential thought processes, psychomotor agitation, insomnia, and speaking with nonsensical, clanging, rapid speech. He had a history of incompletely treated syphilis.

Clinical Presentation

Neuropsychiatric examination revealed prefrontal deficits of echolalia, echopraxia, dysexecutive function, perseveration, and utilization behavior (Figure 1). There were also mesiotemporal deficits of amnesia, hyperorality, and confabulation. Lateralizing features included right-sided Babinski and rooting reflexes. Medication trials of olanzapine in combination with clonazepam and haloperidol in combination with lorazepam, targeting psychosis and catatonia, were of minimal benefit.

Laboratory Studies

Admission workup revealed reactive *T. pallidum*, rapid plasma reagin (RPR) of 1:4, and negative HIV and urine drug screens. Subsequent cerebrospinal fluid (CSF) analysis was remarkable for nonreactive venereal disease research laboratory (VDRL), reactive fluorescent treponemal antibody absorption test (FTA-Abs), 3 nucleated cells with 95% lymphocytosis, glucose of 48, and protein level of 48. An EEG was unremarkable. Brain MRI without contrast showed mild diffuse atrophy and small vessel disease of the subcortical prefrontal (R > L) deep white matter and pons (Figure 2).

Treatment

Because of the history of partially treated syphilis and reactive FTA-Abs, the patient was treated with IV penicillin G. His Montreal Cognitive Assessment score improved from 13 to 22 (30 possible) over a month. He improved enough for antipsychotics and benzodiazepines to be discontinued. After 4 months, a decline was noted in cognition and mood that improved with reintroduction of low-dose haloperidol. Repeat CSF analysis revealed a nonreactive VDRL and FTA-Abs. His brain MRI was unchanged.

Figure 1. Clock drawing task revealing perseveration and dysexecutive function.

Figure 2. Brain MRI without contrast showing mild diffuse atrophy and small vessel disease of the subcortical prefrontal (R > L) deep white matter and pons.
the patient in Case 1 and were minimized for the patient in Case 2. Impairments remained that may have had better outcomes if there had been earlier diagnosis and treatment of syphilis. 

TABLE. A STEPWISE ALGORITHM FOR SYPHILIS TESTING

<table>
<thead>
<tr>
<th>Step</th>
<th>Type of Test</th>
<th>Description</th>
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<tbody>
<tr>
<td>Step 1</td>
<td>Blood nontreponemal tests</td>
<td>Positive when ratio is 1:32 or more. RPR tests for nonspecific Abs to substances released by damaged cells. VDRL detects Abs to cardiolipin.</td>
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<tr>
<td>Step 2</td>
<td>Blood treponemal test</td>
<td>Positive result may detect syphilis when nontreponemal test is negative, especially in early, latent, or previously treated cases. Detects antibodies specific to bacteria (FTA-Abs, MHA-TP, TPPA, TP-EIA, CIA).</td>
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<td>Step 3</td>
<td>CSF nontreponemal</td>
<td>VDRL positive is 100% specific, 27% sensitive.</td>
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<td>Step 4</td>
<td>CSF treponemal</td>
<td>FTA-Abs are 96% specific and 84% sensitive for primary syphilis and ~100% sensitive for later stages. The absence of FTA Abs makes neurosyphilis unlikely.</td>
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Abbreviations: Abs, antibodies; CIA, chemiluminescence immunoassay; CSF, cerebrospinal fluid; FTA-Abs, fluorescent treponemal antibody absorption test; MHA-TP, microhemagglutination assay for *T. pallidum*; RPR, reactive plasma reagin; TP-EIA, *T. pallidum* enzyme immunoassay; TPPA, *T. pallidum* particle agglutination assay; VDRL, venereal disease research laboratory.

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