

## Atypical behavioral and psychiatric symptoms: neurosyphilis should always be considered

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### ABSTRACT

Syphilis still remains a major health concern worldwide because of the possibility of serious medical and psychological consequences, long-term disability, and death. Neurosyphilis (NS) may occur at any stage of infection. Its clinical presentation has been changing over recent years including psychiatric and neurocognitive symptoms. Several recent studies have described cases with these symptoms as the principal signs of NS. We present the case of neurosyphilis with a psychiatric presentation characterized by mood disturbance and auditory and visual hallucinations.

### Keywords

Neurosyphilis; Depression; Hallucinations; Diagnosis; Cerebrospinal fluid

### CASE REPORT

A 48-year-old man was brought to the emergency care unit with a 2-week history of malaise and headache followed by abnormal behavior over the last week, when he presented a depressed mood and an alteration in his mental status with disorientation, uncooperativeness, and self-aggressiveness. Indeed, the patient attempted suicide by trying to hang himself. There was no history of any previous similar episodes, psychiatric diseases, fever, other signs of infection, head trauma, or abuse of illegal substances.

The patient was previously diagnosed with hypertension and diabetes mellitus, and was taking enalapril, metformin and glicazide. There were no reports of tobacco or alcohol consumption, nor any familial history of psychiatric diseases.

On the initial examination, the patient was ruddy, afebrile, and hydrated. His heart rate was 87 beats

per minute; arterial pressure was 140/110 mmHg, respiratory rate was 14 breaths per minute; and capillary glycemia was 237 mg/dL.

The cardiovascular, pulmonary, abdominal, and skin examination was normal. The mental status on admission showed a Glasgow Coma Scale (GCS) of 10, and he was uncooperative, inattentive, and disorientated. His pupils were normal and no motor deficit was detected.

The initial laboratory work-up and the brain computerized tomography were normal. A cerebrospinal fluid (CSF) examination (lumbar puncture) was performed and the results are presented in Table 1. The diagnosis of encephalitis due to the herpes simplex virus (HSV) was suspected and intravenous acyclovir was promptly prescribed, as recommended by Studahl et al.<sup>1</sup>. Polymerase chain reaction for

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**Table 1.** Cerebrospinal fluid examination (lumbar puncture)

	Admission	Day 7	RV <sup>2</sup>
Appearance	Slightly turbid	Slightly turbid	Crystal clear
WBC count	181	303	< 6 WBC/mm <sup>3</sup>
Neutrophil	12	4	Occasional
Lymphocyte	81	87	70%
Monocyte	7	9	30%
RBC count	2	5	0
Total protein	91.1	119.8	18-58 mg/dL
Glucose	121	58	2/3 serum glucose
Lactate	30.1	31.3	< 35 mg/dL
Gram stain	Negative	NA	Negative
Culture	Negative	NA	Sterile

RBC = red blood cell; RV = reference value; WBC = white blood cell.

HSV was not requested due to its unavailability. The electroencephalogram was normal.

After 7 days of anti-viral therapy (acyclovir, 10 mg/kg, three times daily), no clinical improvement was observed, and indeed a new CSF examination resulted in worsened cytological and biochemical parameters (Table 1). Therefore, serum fluorescent treponemal antibody and the Venereal Disease Research Laboratory (VDRL) were requested that resulted positive. The VDRL title was 1/128. The VDRL in the CSF also resulted in the same title (1/128). Table 2 shows the electrophoretic profile of the CSF proteins. Intravenous crystalline G penicillin at a dosage of 24 million units per day in six divided doses over 14 days was prescribed and acyclovir was discontinued on the eighth day. The magnetic resonance imaging (MRI) of the brain revealed oval spots of hyperintensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences involving subcortical white matter of the superior frontal gyri.

Marked clinical improvement was observed after 30 hours of antibiotic therapy. The patient achieved a GCS of 15 and started managing his basic daily living activities. However, he started complaining of visual and auditory hallucinations with persecutory content that were controlled after the administration of risperidone.

At the end of the penicillin therapy, the patient's wife reported his normal behavior. He was discharged to continue medical monitoring in the outpatient clinic.

**Table 2.** Cerebrospinal fluid protein electrophoresis

		RV <sup>3</sup>
Total protein	119.8	18-58 mg/dL
Pre albumin	2	3-7 mg/dL
Albumin	34.6	45-70 mg/dL
$\alpha$ -1 globulin	2	3-7 mg/dL
$\alpha$ -2 globulin	3.4	5-11 mg/dL
$\beta$ -globulin	6	7-13 mg/dL
$\delta$ -globulin	5.3	4-10 mg/dL
$\gamma$ -globulin	46.8	5-12 mg/dL

RV = reference value.

## DISCUSSION

Syphilis is a major global health issue. Worldwide, 36.4 million people were estimated to be infected with *Treponema pallidum*, and 10.6 million new cases of syphilis were reported in 2008.<sup>4</sup> Neurosyphilis (NS) occurs in up to 30% of people with untreated syphilis and may occur at any stage of the infection.<sup>5</sup> Although a decline in the incidence and prevalence of syphilis has been considered as its continuing trend, currently, an increase in new cases of the disease points to the contrary. Meanwhile, the clinical presentation of NS has been changing. Whereas 69% of cases were typical from 1965 to 1984, 86% of cases were atypical from 1995 to 2005.<sup>6</sup>

Neurosyphilis has a wide spectrum of neurocognitive symptoms that, apart from being non-specific, are also common to many neurologic and psychiatric disorders.<sup>5</sup> Early invasion (not necessarily

“involvement”) of the central nervous system (CNS) is thought to occur in many (if not most) patients infected with syphilis.<sup>7</sup> The incubation period can vary from less than 2 years up to 20 years.<sup>5</sup>

NS is divided into early and late disease, and its forms include asymptomatic (most common), meningeal, meningovascular, and parenchymal, which includes general paresis and tabes dorsalis.<sup>6</sup> Early neurosyphilis may be asymptomatic or may present as meningitis or meningovascularitis.<sup>5</sup> Parenchymal NS is the most common presentation among symptomatic cases, presenting with clinical psychiatric picture, including dementia, depression, rage, psychosis, and cognitive impairment.<sup>6,8</sup> Late neurosyphilis tends to affect the brain and spinal cord, typically presenting as tabes dorsalis, general paresis, sensory ataxia, or bowel/bladder dysfunction.<sup>8</sup> The frequency of psychiatric signs and symptoms associated with NS reported in literature ranges from 33% to 86%.<sup>9,10</sup> The most common presenting neuropsychological symptoms comprise personality change and hallucinations (in 48% of patients).<sup>8</sup>

Lin et al.<sup>11</sup> conducted a study on NS showing that 52 of the 169 patients presented psychiatric manifestations, and many of those patients had characteristics of more than one syndrome, including cognitive impairment, personality disorders, delirium, hostility, dysarthria, confusion, disruption of their sleep-wake cycle, fecal and urinary incontinence, dysphoria, paranoia, hallucinations, expansive mood, and mania. These results indicate that NS mimics almost all psychiatric disorders. Costiniuk and MacPherson<sup>5</sup> reported three cases of NS where the treatment was delayed because of the non-specific neurocognitive presentation. The patients presented hyperactivity, sleep disturbances, delusions of grandiosity, seizures, cognitive function impairment, memory alteration, lower-limb weakness and numbness, dysarthria with stuttering speech, and an inability to perform routine activities.

The Centers for Disease Control and Prevention (CDC) has established definition criteria to diagnose neurosyphilis. Two diagnostic categories are described: (i) “confirmed” neurosyphilis, which is defined as present in any stage of syphilis and a reactive CSF VDRL test; and (ii) “presumptive” neurosyphilis, which is defined as present in any stage of syphilis in the presence of a non-reactive CSF VDRL test, CSF

pleocytosis, or elevated protein, and with clinical signs or symptoms consistent with syphilis without an alternate diagnosis to account for these.<sup>8</sup> According to these criteria, our patient had a confirmed NS since he presented symptoms consistent with neurological involvement, and the serologic and the CSF test for VDRL was positive at 1/128.

The CSF is a sensitive indicator of the active neurosyphilitic infection. The CSF abnormalities consist of (i) pleocytosis of up to 100 cells/mm<sup>3</sup>, sometimes higher, which are mostly represented by lymphocytes and a few plasma cells and other mononuclear cells (the counts may be lower in patients with AIDS and those with leukopenia); (ii) elevation of the total protein from 40 mg/dL to 200 mg/dL; (iii) an increase in immunoglobulin G (IgG), usually with oligoclonal banding; and (iv) positive serologic tests. The CSF glucose content is usually normal. The earliest NS change in the CSF consists of pleocytosis and an elevation of protein, which may occur in the first few weeks of the infection before the positivity of the serologic tests. Later on, the CSF changes vary from a spontaneous or therapeutic remission of the disease when the cellularity returns to a normal count followed by the normalization of total protein, and afterwards the IgG concentration reduces. The positive serologic tests are the last to revert to normal.<sup>12</sup>

The CSF abnormalities in patients with serologic evidence for syphilis may occasionally be related to an altered blood-CSF barrier instead of intrathecal immunoglobulin (Ig) production. The Levchik et al.<sup>13</sup> study showed that reactive CSF-VDRL, elevated CSF-white blood cell count, and elevated CSF-*T. pallidum* hemagglutination (TPHA) titers/indices were associated with intrathecal Ig synthesis; whereas non-reactive CSF-fluorescent treponemal antibody absorption, non-reactive CSF-TPHA tests, and CSF-TPHA titers from 1:4 to 1:160 were associated with cases where the intrathecal synthesis was not detected. A classic study from Vartdal et al.<sup>14</sup> has shown that elevated IgG in the CSF is produced intrathecally and has been shown to be adsorbed by *T. pallidum*, usually IgG with oligoclonal banding.

The imaging exams are usually useful for parenchymal evaluation in neurosyphilis, more specifically the MRI. In the study by Zheng et al.,<sup>15</sup> the MRI demonstrated brain atrophy in 87% of cases with psychiatric symptoms, primarily in the frontal

and temporal lobes. However, imaging should be interpreted with caution as normal MRI are also commonly found in those cases.<sup>5</sup>

Historically, the spirochetal infection of the CNS was a great public health concern because of the lack of any specific treatment. Several forms of treatment were proposed, including malariotherapy, which was developed in 1917 by Wagner-Jauregg (Nobel Prize winner in 1927), using a seizure triggered by malaria fever, and other seizure-inducing therapies (e.g. insulin therapy, electroconvulsive therapy) with poor outcomes.<sup>16</sup> Nowadays, syphilis is an easy-to-treat and preventable illness. The treatment of all forms of neurosyphilis consists of the administration of penicillin G, given intravenously in a dosage of 18-24 million units daily (3-4 million units every 4 hours) for 10-14 days. The CDC recommends procaine penicillin, or probenecid and ceftriaxone as an alternative for patients allergic to penicillin. The Jarisch–Herxheimer reaction, which occurs after the first dose of penicillin and is a matter of concern in the treatment of primary syphilis, is of little concern in neurosyphilis; it usually consists of nothing more than a mild temperature elevation and leukocytosis.<sup>12</sup>

The NS follow-up after treatment consists of a neurologic examination and lumbar puncture 3-6 months after treatment and every 6 months thereafter until the CSF white blood cell count achieves the normal limits and the CSF-VDRL becomes non-reactive. The CSF white blood cell count should decline at 6 months after successful treatment, and all CSF abnormalities should resolve within 2 years after treatment. Failure to meet these criteria indicates the necessity of retreatment. Retreatment is also indicated if any follow-up CSF sample shows an increase in the CSF white blood cell count or a four-fold increase in CSF-VDRL titer.<sup>12,17</sup>

## CONCLUSION

This case illustrates the challenge in diagnosing neurosyphilis and the need to consider serologic testing for syphilis in patients with atypical presentation of depression with neurocognitive abnormalities, autoaggressiveness, late onset of mental disorder with acute behavioral symptoms, and lack of history of previous mental illness.

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