

Neurosyphilis in Psychiatric Settings: Three Case Reports



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SUMMARY

Syphilis is a generally sexually transmitted and multisystem disease caused by the spirochete *Treponema pallidum*. All of the organs of the body may be involved during the course of the disease. Neurosyphilis is a clinical form of syphilis with central nervous system (CNS) involvement. While primarily meningeal and vascular structures are involved in early neurosyphilis, parenchymal regions of the brain and spinal cord emerges at later stages of neurosyphilis. It presents with symptoms of meningitis, meningovascularitis, and parenchymal neurosyphilis (presenting as tabes dorsalis and general paresis). Clinically, neurosyphilis can mimic a variety of psychiatric disorders such as depression, psychosis, mania, delirium, personality changes, and dementia. During its progression, syphilis has been defined as “great imitator” making its presentation similar to many systemic or neuropsychiatric diseases. Presently, neurosyphilis is a rare disease that must be kept in mind during the differential diagnosis of neurological and psychiatric disorders. In this article, three neurosyphilis cases with different psychiatric presentations are reported, and literature relevant to syphilis is reviewed.

Keywords: Neurosyphilis, *Treponema pallidum*, psychosis, penicillin.

INTRODUCTION

At one time, syphilis was a life threatening incurable disease. The cause of syphilis was determined when Schaudinn and Hoffman observed *Treponema pallidum* spirochetes using giemsa staining of swab samples taken from secondary lesions (Echeverría 2010). Successful treatment of syphilis was achieved when penicillin was discovered and used in treatments, and the occurrence of the disease was dramatically decreased. Syphilis is often named “the great imitator” in the literature because, it can show a variety of clinical symptoms during the course of the disease (Fitzgerald 1981, Pavia 2008).

A chronic and multisystemic disease, syphilis has been categorized as primary, secondary, and tertiary. Primary syphilis is usually characterized as an ulcerated lesion that usually occurs

3-4 weeks after exposure, settles in the inoculation region, and is usually a painless and clean based chancre. Swabs taken from ulcerated lesions may show spirochetes under dark field microscopy. Ulcerated lesions usually heal on their own without treatment. Secondary syphilis reveals itself 2-12 weeks (4-6 weeks on average) after exposure, and there may not be a sharp transition between primary and secondary syphilis. Primary chancre can be found in one third of the patients with secondary syphilis. In secondary syphilis, fever, lymphadenopathy, alopecia and central nervous system (CNS) involvement can be seen, especially in macular, maculopapular or pustular rash of the palm and soles. Although asymptomatic CNS spread has been demonstrated in early-stage syphilis, CNS involvement is more important in secondary and, especially, tertiary syphilis in terms of being clinically

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symptomatic and making progress. Even though cases of cerebrospinal fluids (CSF) supporting meningeal infections develop in 30.0% of secondary syphilis cases, only 1-2% of them are symptomatic. Lymphocytic pleocytosis, increased protein, normal or low glucose levels can also be observed in CSF. During secondary syphilis, spirochetes can be isolated from skin lesions or CSF based on the clinical condition of the case. After the second phase recovers, the patient enters the quiet, asymptomatic latent period. In one third of the patients that are not treated in the latent period, slow progressing and inflammatory tertiary syphilis involving cases of gum (granulomatous) lesions, cardiovascular, and CNS involvement develop (Domantay-Apostol et al. 2008, Acarel et al. 2002).

CNS involvement of spirochetes infection, although generally defined as neurosyphilis, usually reveals itself in cases of advanced tertiary syphilis. Neurosyphilis may reveal itself in different CNS pathologies and with many clinical appearances. While psychiatric symptoms such as mood changes, psychosis, cognitive impairment, and dementia are more common in the early stages of neurosyphilis, severe neurological deficits can be seen in later stages that are not treated (Bradly et al. 2008, Arisoy et al. 2014).

This article is intended to present neurosyphilis cases with different neuropsychiatric symptoms. The psychiatric reflections of neurosyphilis and its association with the literature will also be discussed.

CASE REPORTS

Case 1: A 40 year old male, primary school graduate that was in his second marriage with one child (from previous marriage was admitted to our clinic. He had been living in Hungary for 14 years and worked with his brother as a restaurant owner. His first marriage lasted only 3 years because of his jealousy towards his wife. He had a 13-year-old daughter from his first marriage. After leaving his wife, he did not have a long-term relationship for nearly 10 years. He met his foreign-national second wife during abroad travel and got married two years ago.

Complaints of swearing, aggression, talking to himself, skepticism, and urinating and defecating himself was documented. Relatives of the patient reported that, while he used to be withdrawn before, he did not sleep for a week, exhibited aggressive behaviors from time to time, did not eat and did not talk much for two days. The patient who was skeptic towards his friends and family and made accusations such as "You cut off and took one of my feet, I'm left with only one foot." He claimed that there was an old man dressed in white in the house and that he was the only one that had seen this old man. His brother who lived with him abroad reported that the patient cried from time to time over the last 2-3 months;

became withdrawn; had a distorted sleeping pattern; got angered very easily; and increased his consumption of alcohol. About a month ago, he went to a hospital in Hungary and was admitted to a psychiatric clinic due to his extreme irritability and psychiatric complaints. He was administered aripiprazole 15 mg/day, alprazolam 0.5 mg/day lamotrigine 100 mg/day, and discharged. After having no change in his complaints, the patient was brought to Turkey for diagnosis and treatment by his relatives. The previous physician ordered venlafaxine 150 mg/day and quetiapine 50 mg/day. With the help of relatives, he used his medication regularly. As his skeptical and aggressive attitude persisted despite the treatment, he was brought to us.

In the psychiatric examination, the patient looked at his age, partially neglected his self-care, and had a flat affect. There was an agitation increase in the patient's psychomotor activity. Due to impaired attention, he could only partially communicate. He was very spatially disoriented, but his time orientation was normal. His speech was rapid with loose association and his answers were not goal oriented. Attention, abstract reasoning, and ability to judge reality were also impaired. The thought content during his appointment included "Why did you imprison me here? Do you want to kill me?" and other questions which showed his persecutory delusions.

He had suspicious neck stiffness during his neurological examination. His pupils were isochoric with flexor bilateral light reflexes +/- and plantar responses. The patient's muscle strength could not be assessed and sensory examination could not be performed due to poor patient cooperation.

At the first assessment, hemogram, routine biochemistry, thyroid function tests (TFT), sedimentation, CRP, anti-HIV HBsAg, antiHBs, HCV, TPHA, VDRL-titration, urine screening of psychoactive substances and activated electroencephalogram (EEG) tests were requested to rule out diagnoses of psychiatric disorders caused by organicity or substance abuse. Lumbar puncture (LP), CSF cell count, and biochemistry were planned for evaluation in terms of encephalitis and meningitis.

The overall follow-up of the patient revealed a fever of 38-39 °C. Hemogram results showed leukocytosis (16.103/ μ L) and neutrophilia (12.103/ μ L). The CSF analysis showed leukocytes 40 /mm³ and erythrocytes 70 /mm³.

The patient's activated EEG results were evaluated within normal limits. In cranial magnetic resonance imaging (MRI), T2-FLAIR series hyperintense foci of 3-4 mm diameters were monitored next to the frontal subcortical white matter and right lateral ventricle occipital (Figure 1).

CSF culture, Ziehl-Neelsen (ZN) staining for the detection of acid-fast bacilli (AFB), BACTEC for mycobacteria, CSF-VDRL, and CSF-RPR tests were requested for the purpose

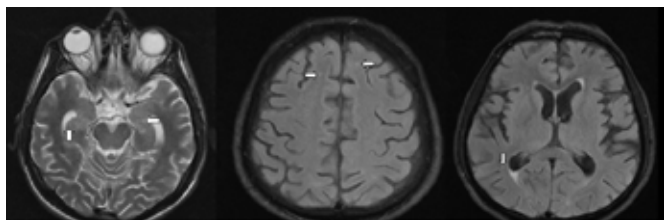


Figure 1. T2-FLAIR series hyperintense foci of 3-4 mm diameter around frontal subcortical white matter and right lateral ventricle occipital in cranial diffusion MRI.

of differential diagnosis. With the pre-diagnosis of bacterial meningoencephalitis, prophylactic administration of ceftriaxone 3x1 g i.m. started for the patient.

In the patient's laboratory results, an increase in liver enzymes (AST: 126 IU/L, ALT: 203 IU/L) and an increase in sedimentation (60 mm/hour) were detected in addition to hemogram neutrophilic leukocytosis. VDRL (Venereal Disease Research Laboratory) and TPHA (Treponemal Pallidum Hemagglutination Assay) serology were positive. Other tests were within normal limits. Abdominal ultrasonography (USG) recommended as a result of internal medicine consultation was evaluated as normal and liver enzyme monitoring was recommended.

A dramatic improvement was observed in the clinical condition of the patient with the second day of the ceftriaxone treatment and his neuropsychiatric signs and symptoms regressed. Based on the patient's disease history, clinical condition, neuropsychiatric examination, and laboratory findings, he was diagnosed with meningovascular neurosyphilis. His antibiotherapy was completed in and ceased after 14 days. During the patient's discharge, the assessment revealed that his self-care was good, his mood was euthymic, cooperative, and orientated, in addition to his normal thought processes, perception, and ability to judge reality. The patient was discharged with clinical improvement.

Case 2: A 59 year old male divorced, primary school graduate was admitted to our clinic. He could not keep a job for a long duration and lived alone in Istanbul. It is stated that he had many suspicious extramarital affairs in the past. The patient used alcohol for 40 years and first applied to AMATEM for alcohol addiction. The patient's history revealed that he did not have any serious disorders except for alcohol addiction throughout his life and that this was the first time he was admitted to a hospital.

It was stated that the patient consumed roughly 75 cl raki a day and consumed 3-4 bottles of high alcohol beer a day during the past 3 years. Until recently, he did not try to quit alcohol or cure his alcohol addiction on his own. We learned that, while having a limited social support, the patient did not get along with his peers and mostly had alcohol consuming friends like him or was on his own. Following an

intramuscular thiamine and pyridoxine replacement to the patient upon admission, oral treatment of diazepam 40 mg/day and quetiapine 300 mg/day started. Vitamin B complex and folate were replaced orally. On the third day of hospitalization, he restlessly wandered around and, from time to time, he appeared to be making gestures as if he was picking things up and hummed to himself. It was reported that he shouted in his sleep and tried to push something with his hands.

In the patient's psychiatric examination, the patient looked his age and partially neglected self-care, and had a furious mood. He was spatially oriented but severely disoriented in time. It was detected that he had loose association of thoughts and difficulty being goal oriented. Thought content included non-systematic persecutory delusions. It was observed that the patient who scored 13/30 at the mini mental state assessment test had a low memory performance.

In the patient's neurological examination, he was conscious, appeared confused and his speech was slightly dysarthric. His pupils were isochoric, while his light reflexes ++ and plantar responses were flexor bilaterally, deep tendon reflexes were normoactive. The patient who did not have any balance and walking faults had full muscle strength, normoactive deep tendon reflexes and normal cerebellar test.

In the initial plan all the routine tests and anti-HIV, HBsAg, anti-HBs, HCV, TPHA, VDRL-titration, screening of psychoactive substance metabolites in the urine and cranial MRI was requested for the patient who was being considered for delirium tremens diagnosis due to alcohol withdrawal. As the TPHA test was positive after the tests, neurosyphilis was suspected. The patient VDRL and cell count in CSF were performed. VDRL test was positive and the CSF analysis resulted in 3 lymphocytes /mm³. Cranial MRI showed ischemic gliotic foci in both periventricular white matter along with cerebral and cerebellar atrophy.

The patient diagnosed with neurosyphilis was daily administered 24 million units of crystallized penicillin G parenterally for 3 weeks with the recommendation of infectious diseases specialist. Quetiapine 25 mg/day was added to the treatment from time to time due to excitation and was increased to 400 mg/day based on the clinical condition. In the patient's psychiatric examination for discharge, he was conscious, cooperative, disorientated in time, good self-care, fluent and objective speech, thought process was logical and linear. The patient who had an euthymic mood, did not have hallucinations or delusions in the perception and thought content. The Mini-mental state examination was assessed as mild cognitive impairment. The discharge was made with clinical improvement.

Case 3: A 55 year old married male, primary school graduate was admitted to our clinic. The patient, who lives with his family in Kocaeli, works as a truck driver between the

Netherlands and Iraq. He experienced excessive irritability and outbursts of anger over a 2 year period. His relatives reported that he seeing things, ran away when he saw the police, was skeptic and had thoughts that someone from the television was controlling him. In this process, the patient's complaints increased. For the last 1-2 months, the patient started to speak less and became withdrawn. The patient was reluctant to communicate with others. His relatives noticed when they tried to communicate with him that his speech was improper and partially obscured. The patient's gait disturbance increased over time and he started to lose his day to day functionality and became bedridden.

In the patient's psychiatric examination, the patient, who looked his age and neglected his self-care, was confused. He was indifferent to others and did not communicate with them. Judgment and abstract thinking could not be assessed. A test of memory could not be performed. According to information received from his relatives, we learned that the patient's thought content from 7-8 months ago included someone from the television controlling and managing his brain and persecutory delusions.

In the patient's neurological examination, he was conscious, uncooperative, disoriented in person, place, and time and seemed apathetic. In physical examination, the eyes were on the midline and movements in all directions of both eyes were normal. His pupils were isochoric, while his light reflexes +/- and plantar responses were flexor bilaterally. His deep tendon reflexes were hyperactive in all four extremities. The patient could not sit or walk without assistance. As the patient was not cooperative; therefore, sensory and cerebellar system examination could not be evaluated.

On clinical admission, his vital signs were stable. His fever was measured as 36.5 oC. Along with the routine tests, Anti-HIV, HBsAg, anti-HBs, HCV, TPHA, VDRL-titration, and urine screening of psychoactive substances were requested. While testing the patient for organic causes in the cranial MRI, chronic ischemia secondary focal damage areas in both cerebral hemisphere white matter, two ischemic gliosis foci in left frontal lobe, and minimal expansion in both sides of the 3rd ventricle were detected. EEG was considered compatible with the common bioelectrical disorganization and mild neuronal hyperexcitability in both frontal areas. As the patient's follow-up TPHA and VDRL results were positive, VDRL and cell count in CSF were requested. The CSF examination revealed lymphocytes 25/mm³, protein 171 mg/dl, and positive VDRL. The patient, who was considered for neurosyphilis, was administered 24 million IU/day crystallized penicillin G treatment which was maintained for 20 days, with the recommendation of an infectious disease specialist. It was observed during the treatment that the patient's general condition partially healed. Due to his restless behavior, quetiapine 25 mg/day was added to the penicillin treatment. During the

patient's discharge, the assessment revealed that he was conscious, cooperative, received single-step orders, had trouble performing more complex orders, could sit without support, and had partially recovered speech and walk. The patient was discharged with partial recovery.

DISCUSSION

Neurosyphilis, or syphilis with CNS involvement, is observed in secondary and tertiary stages. Meningeal and meningovascular involvement is more apparent in the early stages of neurosyphilis while, parenchymal involvement is more apparent in later stages.

Only 1-2% of secondary syphilis cases are symptomatic. Symptomatic cases appear with cases of meningitis and meningovascularitis. Tertiary syphilis is observed in only one third of the patients transitioning from the secondary phase to the latent period. While meningeal and meningovascular involvement is usually present in the early stages of tertiary syphilis, parenchymal involvement becomes more dominant in later stages.

Syphilitic meningitis, meningovascular syphilis, parietic neurosyphilis, and tabes dorsalis are the clinical cases of different pathologies including meningeal invasion, obliterative endarteritis, and parenchymal invasion, respectively. Meningeal and meningovascular syphilis makes up approximately 10.0% of neurosyphilis cases and generally reveals itself 4-7 years after the initial infection. Vascular involvement and focal findings based on the location of strokes and involvement, sleep deprivation, fluctuations in consciousness, personality changes and emotional liability can be seen. Headaches are frequent due to meningeal involvement. Parietic neurosyphilis and tabes dorsalis are the clinical cases that start 15-20 years on average after the initial infection and go away after the involvement of neurosyphilis, CNS, and the spinal cord. In parietic neurosyphilis, psychiatric diagnosis is vital due to the possibility of many clinical situations such as emotional liability, personality changes, mania, paranoia, psychosis and dementia (Bradly et al. 2008, Arisoy et al. 2014). Due to the widespread use of antibiotics and HIV infection today, it is reported that overlapping and atypical clinical situations are more often observed (Hooshmand et al. 1972, Johns et al. 1987, Musher et al. 1990).

The suspicious neck stiffness and meningitis pre-diagnosis in our first case gave rise to the tertiary neurosyphilis diagnosis where meningeal and meningovascular involvement was apparent. The good response to the antibiotherapy treatment supports the early stage CNS involvement of neurosyphilis. In addition, cranial MRI showed hyperintense foci signaling and parenchymal involvement. The patient's clinical appearance was withdrawn in the early stages, which was followed

by behavioral changes, paranoid delusions, and occasional excitation. Thus, that the observed disorganized behavior and cognitive impairment became apparent. When findings and clinical appearance were considered altogether, it was thought that parenchymal involvement accompanied meningeal and meningovascular involvement.

In our second case, alcohol addiction and neurosyphilis were detected. Neurosyphilis and delirium tremens case overlapped and made diagnosis as well as treatment complicated. The patient presented with irritability, lower memory performance, hallucinations, and paranoid delusions. Delirium tremens diagnosis alone was not sufficient for explaining case. The CSF VDRL positivity after the serum TPHA serum positivity enabled the additional diagnosis of neurosyphilis. While the nonspecific periventricular ischemic gliotic foci in cranial MRI alone did not explain the syphilitic vasculitic case, syphilitic obliterative endarteritis should be kept in mind. It was thought that cerebral and cerebellar atrophy was due to the loss of white and grey matter volumes caused by chronic alcohol use (Bühler and Mann 2011). The rapid progress of the case could be related to the malnutrition and immune system suppression associated with chronic alcohol use of the patient. In addition, the accompanying clinical conditions were observed to overlap (Molina et al. 2010). Alcohol use also causes risky sexual behavior, since alcohol abuse and addiction increase the risk of sexually transmitted diseases (Saggurt et al. 2010, Muchimba et al. 2013).

Third clinical case indicated the presence of more severe process. Late stage neurosyphilis seem to be compatible with the common parenchymal involvement. Cranial MRI showed chronic ischemic focal damaged areas. The patient's clinical case included a progressive cognitive impairment and the patient became progressively bedridden. Dementia cases and findings that suggest CNS involvement with parenchyma impact or, in other words, paretic neurosyphilis are important to consider. The fact that the response to treatment was partial showed that the severity and irreversibility of the damage to the parenchymal neurons. Paretic neurosyphilis is the parenchymal form that occurs 10-20 years after the initial infection and psychiatric symptoms are insidious. Symptoms start with emotional liability, impaired attention, and forgetfulness. Personality changes, euphoric mania, paranoia, hallucinations and delusions are observed in the following stages. In untreated patients, dementia develops five years after the initial symptoms starts and this process results in death (Simon et al. 2007). The differential diagnosis of the cases of dementia and cranial involvement must be considered (Gurses et al. 2007).

The notifications regarding the psychiatric manifestations of neurosyphilis in the literature are usually in the form of case reports. Timmermans and Carr (2004) reported that approximately 51.0% of the 161 neurosyphilis cases were neuropsychiatric symptoms. Danielsen et al. (2004) reported that the

reason for admission of 36.0% of the 92 cases was neurological symptoms and it was psychiatric symptoms for 12.0%. Most of these cases were followed up with parenchymal neurosyphilis diagnosis. Roberts and Emsey (1992) reported that among 21 cases that were hospitalized due to psychiatric symptoms: 76.0% had personality changes, 67.0% had psychotic symptoms, 62.0% had cognitive impairment, 52.0% had aggressive behaviors, and 38.0% had outburst symptoms. Neurosyphilis can mimic almost any neurologic and psychiatric disorder (Kohler and Johnson 2005).

Early stage diagnosis and treatment are important in neurosyphilis. Response to the treatment is related to the state of the neurological damage. Cognitive and psychiatric symptoms of paretic neurosyphilis in the early stages can be rehabilitated with treatment. However, response is poor and the impact of the disease are permanent in late stage cases.

Neurosyphilis diagnosis was based on clinical findings, CSF examination (CSF VDRL, leucocyte and protein), treponemal (TPHA, FTA-ABS), and nontreponemal (VDRL, RPR) serological tests. Treponema pallidum is quite sensitive to penicillin and penicillin is used in every stage of syphilis effectively. Eighteen to twenty four million units/day intravenous crystallized penicillin G (3-4 million units every four hours) treatment is recommended for 10-14 days.

CONCLUSION

Based on the case reports and the information we provide herein:

1. Neurosyphilis, which is deemed to be rare due to the widespread use of antibiotherapy today, may cause a wide range of clinical situations. It is important to assess neurosyphilis according to the differential diagnosis when dealing with suspicious cases.
2. Secondary and early stage tertiary neurosyphilis can be treated effectively with parenteral penicillin. Early diagnosis and treatment of disease may reverse the neuropsychiatric clinical situation.
3. It must be noted that neurosyphilis may be accompanied with alcohol and substance abuse disorders.

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