



# A Neurosyphilis Case Presenting with Cognitive Dysfunction, Epileptic Seizures, High Signal Intensity and Significant Atrophy in Left Amygdala/Hippocampal Region

*Kognitif Bozukluk, Epileptik Nöbetler, Sol Amigdala/Hippokampal Bölgede Sinyal Artışı ve Belirgin Atrofi ile Seyreden bir Nörosifilis Olgusu*

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## Summary

Syphilis is a sexually transmitted, chronic, multisystemic disease. Central nervous system involvement occurs in secondary and tertiary stages. Neurosyphilis presents itself as meningitis or meningovascularitis in secondary stage, and general paresis or tabes dorsalis in tertiary stage. In the antibiotic era, however, instead of classical neurosyphilis atypical forms with intertwined clinical symptoms started to occur more frequently, making the diagnosis more difficult. In this article, we present a neurosyphilis case who applied to the clinic with generalized tonic clonic convulsions resulting in multiple traffic accidents. The characteristic of this case is the ongoing memory problems due to attentional dysfunction as shown in neuropsychological tests despite the penicillin treatment and the presence of a high signal intensity and significant atrophy in his left amygdala/hippocampal area seen in cranial magnetic resonance imaging. (Turkish Journal of Neurology 2014; 20:55-9)

**Key Words:** Neurosyphilis, amygdala/hippocampal area, high signal intensity, seizure, dementia

## Özet

Sifilis, genellikle cinsel yolla bulaşan kronik, multisistemik bir hastalıktır. Merkezi sinir sistemi tutulumu sekonder ve tersiyer evrelerde görülür. Nörosifilis, sekonder evrede sifilitik menenjit ve meningovaskülit; tersiyer evrede ise genel parezi (sifilitik demans), tabes dorsalis gibi tablolarla karşımıza çıkabilir. Ancak antibiyotik kullanımının yaygınlaşması ile birlikte klasik nörosifilis formları yerine belirtilerin iç içe geçtiği atipik formlar daha sık görülmeye başlanmış, bu da tanı konmasını zorlaştırmıştır. Bu yazıda, trafik kazalarıyla sonuçlanan jeneralize tonik klonik nöbetler geçirerek kliniğe başvuran bir nörosifilis vakası sunulmuştur. Bu vakanın özelliği, penisilin tedavisine rağmen nöropsikolojik testlerde de gösterildiği üzere dikkat azalmasına bağlı süregelen bellek sorunlarının olması ve manyetik rezonans görüntülemeye sol amigdala/hippokampal bileşkekte sinyal artışı ile belirgin bir atrofisinin saptanmasıdır. (Türk Nöroloji Dergisi 2014; 20:55-9)

**Anahtar Kelimeler:** Nörosifilis, amigdala/hippokampal bileşke, sinyal artışı, nöbet, demans

## Introduction

Syphilis, is a chronic, multisystem disease caused by the spirochaete *Treponema pallidum* that is transmitted either sexually or from mother to child (1). While its incidence rate decreased with the invention of penicillin, it rose again during the AIDS epidemic in the 1980's (2). Throughout the primary, secondary and tertiary stages of the disease, central nervous system (CNS) is affected more visibly during the secondary and tertiary stages (3).

Primary syphilis is characterized by the skin lesion called chancre that is seen in the infection zone at around 3-90 days after contact with the organism. Secondary syphilis, developing at 2-12 weeks after the contact is a widespread infection presenting with fever, muscle-skeletal pain, widespread lymphopathy and rashes. The organism infiltrates CNS within 3-18 months. One third of the secondary syphilis patients show meningeal infection in the cerebrospinal fluid (CSF) but only 1%-2% of the cases become symptomatic. Following the treatment in the second stage, the disease becomes latent and asymptomatic, detectable only through serology. Cerebrospinal fluid is often normal at this stage, and any abnormalities suggest asymptomatic neurosyphilis. When left untreated, 1/3<sup>rd</sup> of the patients develop tertiary syphilis. The early stage manifestation of tertiary syphilis emerges 5-10 years after the primary infection while the late state manifestation emerges 10-30 years after. The early stage is often in the form of a meningovascular disease while the late stage is general paresis/syphilitic dementia (GP/SD) or tabes dorsalis (TD) (1).

With the prolific use of antibiotics, this high GP/SD ratio has dropped and meningeal and meningovascular forms began to be more prevalent. Now instead of the classical NS cases, there appeared different combinations where different clinical profiles entwine (1). These atypical profiles rendered the NS diagnosis very hard to make based on clinical findings alone (4).

Even though the incidence rate of NS has been low in the recent history, the researchers emphasize that the disease still remains to be a significant issue (2). In the developed world, NS is commonly seen in human immunodeficiency virus (HIV) positive patients (1). However, NS cases are still being reported in Turkey in HIV negative patients. In this paper, we present a case of atypical NS that was manifested 6 years after transmission in a HIV negative patient.

## Case

Forty six year old, elementary school-educated, married, male who worked as a truck driver consulted in our clinic to file for early retirement due to disability. Being laid off 2 months ago, the patient complained about forgetfulness and fainting.

Having fainted six years ago in his workplace the first time, the patient reported not remembering fainting itself, but blacking out and feeling light headed. His relatives reported that he lost consciousness and became stiff without any foaming in the mouth or urinary incontinence, but he would feel disoriented upon regaining consciousness. Having fainted six times in the past year, it was reported that his episodes 3 and 11 months ago occurred when he was driving his truck and they both resulted in traffic accidents. The patient reported forgetting recent events, difficulty in learning new things, concentration problems, frequent balance

problems during walking and poor navigation skills when he is driving, making him unable to perform his job. Being laid off after the accident that happened 3 months ago, he reported loss of morale, shortness of temper, sleep disorders and maximum 5 hours of sleep every night.

The patient mentioned that he has skin lesions following the unprotected sexual intercourse he had 11 years ago, and started fainting at work 6 years after that. According to the family's reports, the patient was admitted to a neurology clinic for the continuing memory and speech impairments. Due to the lack of cells in his lumbar puncture (LP) but the protein level being 70 mg/dl with normal glucose, positive CSF VDRL, *Treponema pallidum* antibodies (TPA) titration 1/5120, the patient was diagnosed as NS and put on penicillin treatment. The patient was put on antiepileptic after he developed tonic clonic seizures when he was being monitored. He scored 15/30 in his first Mini Mental State Evaluation (MMSE) in that stage. His cranial contrast magnetic resonance imaging (MRI), thyroid tests and antibodies were normal and HIV was negative. Even though his CSF parameters did not change after the treatment, his MMSE increased to 22/30. At the three-month follow-up, he had a wide-stance gait and he was still experiencing memory problems. At the six-month follow-up, the dose of penicillin was increased due to the lack of decline in the TPA titration. At the one-year follow-up, TPA had declined to 1/2560 and then 1/1280 at the end of 1.5 years. At this stage, however, his second MRI showed expansion of cerebral sulcus and deepening of cerebella folia, dilation of the 3<sup>rd</sup> and lateral ventricles and cisterna magna due to atrophy. At the four-year control, it was reported that he was laid off due to fainting while he was on the wheel and causing traffic accidents twice in six months.

In his psychiatric evaluation, he was conscious, cooperative, oriented with apparently intact personal care, psychomotor functioning and motivation for treatment. The patient could not count backwards with complete success due to loss of concentration and his speech was dysarthric. His working memory was normal but recall memory was impaired (1/3 recall). His long-term memory was intact. His mood was depressed and his thoughts supported this state. There were no hallucinations or enormity; his associations were normal, rational and goal oriented. His judgment was intact; his vocabulary and arithmetic skills were adequate but he had trouble with abstractions. He interpreted the proverb "Drops make a lake" as "Getting wet". His neurological examination did not show meningeal irritation findings; cranial nerves were intact and the muscle strength was preserved; DTR was normoactive; His plantar reflex was flexor; his sensory, extrapyramidal, cerebellar and autonomous system examination and stance and gait were normal. The patient was still using phenytoin sodium 3x1, fenofibrate 1x1, and benzathine penicillin 1.2 million units/20 days. He scored 42 in the Beck Depression Inventory (BDE) and 24.30 in MMSE.

The patient was started on sertraline 50 mg/day for his depression and he completed the neuropsychological test battery (NPT) after his depression had subdued. In this test, verbal memory processes test indicated a difficulty in recall and a severe disturbance secondary to attentional deficit. His attentional span was mildly narrowed. In the categorical and verbal fluency tests which assess the attention maintenance, it was seen that his

attention was severely impaired. He also showed mild deficits in inhibiting incorrect answers and visuospatial processing. These results suggested that he possibly had a memory disorder secondary to attentional deficit and that this profile is in line with a severe disruption in the attentional processes mediated by the frontal system.

In accordance with the NS chronic stage involvement, his contrast and diffusion weighted cranial MRI showed signal increase, substantial volume loss in the left amygdala/hippocampal complex and minimal cerebral-cerebellar atrophy (Figure 1). His EEG showed widespread disorganization. Doppler and echocardiography were normal and there were no cardiac involvement.

## Discussion

There are few examples of reported cases of NS in Turkey (5). With the notion that NS cases are becoming increasingly rare due to the availability of antibiotics, physicians became less familiar with the disease which presents an obstacle for the appropriate diagnosis of the disease, resulting in misdiagnoses (6,7). Neurosyphilis should always be kept in consideration in the cases of early onset cognitive decline or late onset epileptic seizures.

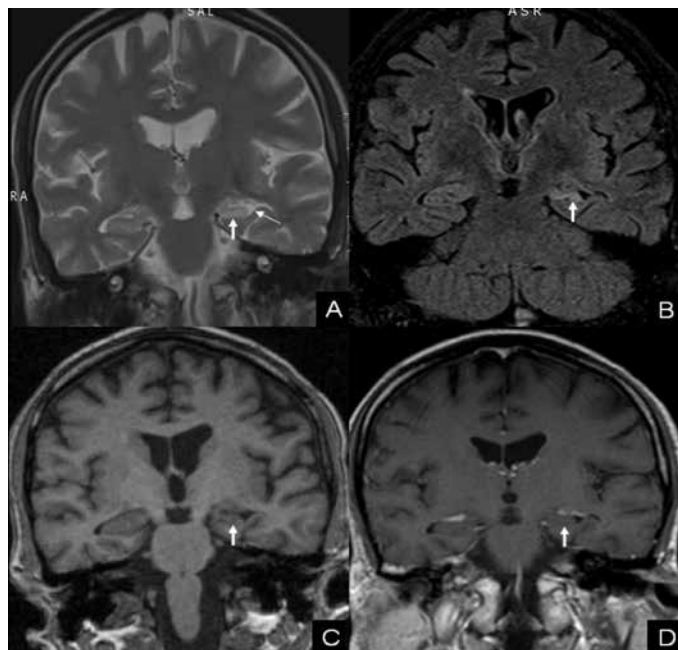
Our 46-year-old patient can also be considered young patient, who had tonic-clonic epileptic seizures, dysarthric speech and visible cognitive impairment starting at age 40. The rate of seizures in NS are reported as 8.5%-60% (8). Sinha et al. reported this rate as 25% and none of those cases had a known history of epilepsy. For this reason, sudden emergence of epileptic seizures in a non-epileptic person should always bring NS to mind. Similar to our

cases, seizures were presented as the first symptoms of the disease in 1/4<sup>th</sup> of Sinha et al.'s participant group (9). Electroconvulsive therapy abnormalities were seen in 61.5% of the NS cases (8). A visible sluggishness in the EEG or epileptiform discharges can be seen and these discharges may respond to penicillin (9). We observed widespread disorganization in our case. While the seizures are often seen in the GP stage, in Sinha et al.'s series, they were primarily (76.7%) seen in the meningovascular stage (9).

Neurosyphilis involves meninx and blood vessels in the early stage (5-10 years) and brain and spinal cord in the late stage (10-30) (3). Meninx involvement is manifested as meningitis and it typically appears within the first 2 years. The meningitis form is the least common form and it is seen only 0.3%-2.4% of all NS cases (3). Meningovascular involvement is characterized by hemiparesis, aphasia, vision loss and confusion caused by cortical and subcortical infarcts (6). Cerebral parenchyma (brain) is involved in the general paresis due to chronic meningovascularitis (1,7). Several different psychiatric symptoms that mimic the profile for multiple psychiatric diseases, such as progressive dementia, mania, depression, emotional lability, personality changes, paranoia, feelings of grandeur, enormity, hallucinations, illusions and inappropriate behaviors. For that reason, the disease was given the nickname "the great imitator". During the onset of the disease, it is possible to observe misdemeanors committed in foolish and reckless fashion. This stage is also called medicolegal stage for that reason (6). The most common problem, however, is the dementia characterized by memory loss, decision making difficulty, and emotional lability (1). The cognitive breakdown starts generally 15-20 years after transmission (around the ages 35-40). General paresis also shows neurological abnormalities like apathy, dysarthria, echolalia, small tremor in tongue-mouth-face and hands, hyper-reflexia, myoclonus, seizures, hypomimia, chorioretinitis, optic neuritis and irregular pupils with reduced light-reflex (Argyll-Robertson pupils). Seizures, dementia and quadriplegia characterize the late stage.

In general paresis, it is possible to see frontal and temporal atrophy, subcortical gliosis, and ferritin increase in basal ganglia in the cranial MRI. It results in mortality within 3-5 years if it is left untreated. The clinical outcome of the treatment depends on the nature and propagation of the neuropathology at the time of treatment onset. If the inflammatory reaction only causes cerebral dysfunction, the outcome is generally positive; when sufficient number of cerebral neurons are damaged through the infection, however, the treatment may help with the infection but the cerebral function will not be restored (1). In the following years, the overall situation worsens and results in death following the emergence of gait disorders, loss of sphincter control and cachexia. Romberg's sign, visceral pain and incontinence are also seen in the profile (6). Tabetic and parietic syphilis can also be seen together (taboparesis).

The fact that our case had a history of genital lesion 11 years ago suggests that the patient might have gone through the primary syphilis stage. The reported lack of symptoms until 6 years after transmission, however, suggests that the secondary syphilis stage might have gone asymptotically. Since the first symptoms appearing 6 years after the transmission (at the age 40) were generalized epileptic seizures, dysarthric speech and apparent cognitive decline (MMSE=15/30), the NS profile seems to be



**Figure 1.** A-D. Coronal TSE T2 weighted (A), coronal FLAIR (B), pre-contrast and post-contrast TSE T1 weighted (C, D) showing diffuse signal increase, volume decrease with respect to the other side of the left mesial temporal area, and minimal dilation in the secondary lateral ventricle left temporal horn (A) (thin arrow)

congruent with GP. Even though the balance disorder described for the past 2 years and wide-stace gait indicated the possibility of TD, the lack of spinal cord involvement in the neurological examination rules out this explanation. While GP emerges at the late stage, it appeared 6 years after transmission in our patient.

The first MRI findings in the form of atrophy emerged 7 years after the transmission and were transformed into signal increase in left amygdala/hippocampal complex and apparent volume loss when he came to our clinic 11 years after the transmission. A limited number of NS cases were reported with lesions causing signal changes in the temporal lobe (13,14). The case deserves attention in this case. There is a large variety of MRI findings associated with NS in the literature including mild frontocortical, cerebellum and brainstem atrophies, cortical-subcortical ischemic gliotic foci, infarctions, nonspecific white matter changes, leptomeningeal contrast involvement, syphilitic gummas, leptomeningeal granulomatosis, arthritis, and high signal intensity on the frontal region (15). The most common MRI finding, however, is the cortical atrophy and gliosis. Meningovascular lesions present themselves as cortical-subcortical infarcts, leptomeningeal contrast involvement, meningitis and arthritis but none of them were reported on a limbic region (16).

To date, there have only been 13 reported cases of medial temporal lobe hyperintensity (13,14,17). Five of these lesions were bilateral and 8 were unilateral. All of the cases were males who got symptomatic after 2 years. Even though the symptoms resembled late stage NS, the prognoses were generally positive and the lesions disappeared after penicillin treatment (13,19-20). In some other cases there were also reports of medial temporal region T2 signal intensity increases that responded positively to treatment (19). Typically, the psychiatric problems associated with bilateral medial temporal T2 signal increase and subacute onset memory problems are seen in the paraneoplastic limbic encephalitis but it is possible to see them also in herpetic and non-herpetic encephalitis, malign lymphoma and HIV encephalopathy (21). On the other hand, they can also be seen in NS patients (17). In such cases, however, contrast involvement in T1 sequences like those in herpes encephalitis or paraneoplastic limbic encephalitis was not reported (14). For that reason, mediotemporal lesion and hyperintensity in T2 should require a careful differential diagnosis that includes NS (14).

The pathological reasons behind the medial temporal T2 signal increase are still unknown (17). They could be the result of vasogenic or cytotoxic edema, inflammation, meningovascularitis or microglial hypertrophy. Vasogenic edema might develop due to the increased permeability of the blood-brain barrier during the meningitis stage of NS. In the meningovascularitis stage, ischemic cytotoxic edema or, in more serious conditions, irreversible infarctions or gliosis may develop due to small vessel involvement (18) but no limbic lesions were reported in the meningovascularitic stage (16). In the general paresis stage, microglial hypertrophy due to parenchymal inflammation can be observed. The temporary T2 hyperintensities can be alleviated through penicillin treatment but the T2 hyperintensities due to vasculitis may not respond to treatment and can cause the development of seizures (18). For this reason, repeated MRI scans are useful in the differential diagnosis of the mediotemporal lesions. In a Turkish case study that used repeated MRI scans, it was reported that the left mediotemporal signal increase and the accompanying

psychotic symptoms responded completely to penicillin treatment (22). In our case, however, the signal increase in amygdala/hippocampal complex persevered over 6 months through penicillin treatment and the epileptic seizures did not disappear. Sinha et al. (9) reported a higher likelihood of MRI abnormalities in NS cases with seizures than those without (86% versus 71%) and that they also had higher rates of diffuse atrophy, medial temporal lobe signal changes and meningeal contrast involvement, much like in our case.

We also detected cerebral-cerebellar atrophy in our case. Cortical atrophy is one of the most common signs of NS. The relatively preserved state in our case might be the result of a positive response to the treatment. However, there is no reliable predictor for the post-treatment prognosis of NS. Some cases in the literature showed that temporal MRI abnormalities improve with treatment. Having said that this was not the case with our patient, further studies will show if the clinical improvement is necessarily accompanied by the improvement in such MRI lesions. Early diagnosis and aggressive treatment plans will gain much more importance after it is conclusively shown that MRI abnormalities can be reversed with treatment and maybe become a predictive tool for the prognosis of general paresis.

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