

## PITFALLS IN THE DIAGNOSIS OF NEUROSYPHILIS - CASE REPORT AND LITERATURE REVIEW

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**Abstract:** Neurosyphilis can affect all the major parts of the nervous system as the meninges, brain, spinal cord, nerve roots, cerebral and spinal blood vessels. The clinical manifestations are polymorphic and represent an important diagnostic challenge. The neurological symptomatology of syphilis may develop within weeks/months of the initial infection or, in some cases, it takes decades to appear. We present a case of a 64-year-old male patient, with classical vascular risk factors, who presented a typical symptomatology of right middle cerebral artery stroke, but who developed later, in the next 3 months unusual manifestations as central pain, psychiatric symptomatology (depression and cognitive impairment) and amyotrophy in the paralyzed upper limb. This manifestation prompted us to perform additional workup for differential diagnosis. Based on the serum and cerebrospinal fluid serology results, the diagnosis of neurosyphilis was established. Despite the proper treatment, the evolution was towards rapid aggravation and death. We would like to highlight the fact that despite the dramatic decline in the incidence of neurosyphilis since the 20<sup>th</sup> century, the neurologist need to remain aware of the clinical presentation, diagnosis and treatment of this disease because new cases are still occurring.

**Cuvinte**

neurosifilis, vascular amiotrofie

**cheie:**

accident cerebral,

**Rezumat:** Neurosifilisul poate să afecteze toate structurile majore ale sistemului nervos: meningele, creierul, măduva spinării, rădăcinile nervoase, vasele cerebrale și spinale. Manifestările clinice sunt polimorfe și reprezintă o provocare diagnostică. Simptomatologia neurologică poate să se dezvolte în săptămâni/luni de la infecția primară sau în unele cazuri chiar decenii. Prezentăm cazul unui bărbat în vârstă de 64 ani, cu factori de risc vasculari clasici, care s-a prezentat cu simptomatologia unui accident vascular cerebral ischemic silvian drept, dar care ulterior, în următoarele 3 luni dezvoltă manifestări atipice, ca durere centrală, simptomatologie psihiatrică (depresie, deteriorare cognitivă) și amiotrofia membrului superior paralizat. Aceste manifestări ne-au determinat să efectuăm investigații suplimentare în vederea diagnosticului diferențial. Pe baza examenului serologic din sânge și lichidul cefalorahidian a fost stabilit diagnosticul de neurosifilis. În ciuda tratamentului adecvat, pacientul prezintă o progresie rapidă a simptomatologiei și decedează. Pe baza acestui caz dorim să subliniem faptul că în ciuda scăderii dramatice a incidenței neurosifilisului după secolul 20, neurologii trebuie să cunoască bine prezentarea clinică, diagnosticul și tratamentul acestei boli, având în vedere că noi cazuri continuă să apară.

### INTRODUCTION

Syphilis comes from the Greek word syphlos, meaning crippled or maimed.(1) It was first described in a Latin epic poem, "Syphilis, sive morbus gallicus", written by Girolamo Fracastoro in his work "De contagione et contagiosis morbis" in 1530. It is a sexually transmitted disease caused by *Treponema pallidum*, a spirochete that was first described in March 1905, by the zoologists Fritz Schaudinn and Erich Hoffmann in the Department of Dermatology at Berlin Charite Hospital in a syphilitic pustule and in a lymph node.(2) The infection, if untreated, passes through primary, secondary, latent and tertiary stages. The most frequent presentations of tertiary syphilis are: neurosyphilis (NS), cardiovascular syphilis and late benign syphilis. NS is defined as an infection of the central nervous system caused by *Treponema pallidum* penetration of the blood-brain barrier. It can occur any time after the initial infection. Early neurosyphilis involves cerebrospinal fluid (CSF), meninges and vasculature (asymptomatic meningitis, symptomatic meningitis and meningovascular disease), whereas

late neurosyphilis affects the brain and spinal cord parenchyma (general paralysis of the insane and tabes dorsalis).

Each form of neurosyphilis has characteristic clinical findings, but these entities frequently overlap.(3)

Syphilitic amyotrophy, or muscular atrophy of syphilitic aetiology, was first described by Ballet (1894). It is due to a progressive degeneration of the anterior horn cells in the spinal cord. Spinal syphilis can be classified into: meningeal (pachymeningitis, vascular, meningomyelitis) and parenchymatous (tabes dorsalis). Syphilitic amyotrophy can result from any of this forms, but it is a term usually reserved for the muscle atrophy caused by meningomyelitis.(4)

We present a case of neurosyphilis with atypical and rare clinical manifestation.

### CASE REPORT

A 64-year-old male patient, with a history of hypertension and type 2 diabetes, under antihypertensive and antidiabetic treatment, but without antithrombotics presented

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suddenly in December, 2013 left sided hemiparesis. His physical examination revealed only elevated blood pressure, 190/90mmHg, otherwise, it was unremarkable. The neurological examination upon admission evidenced left central facial palsy, grade 3 left hemiparesis, exaggerated deep tendon reflexes and extensor plantar response on the left side, left hemihypoesthesia. The patient arrived in emergency room 5 hours after the symptoms onset, so he was not a candidate for intravenous thrombolysis.

The laboratory examinations (complete blood count, liver enzymes, lipid panel, urea, creatinine, sodium, potassium, and erythrocyte sedimentation rate) were normal except for the blood glucose which was slightly elevated (133-135mg%).

Brain computed tomography was performed, which showed only diffuse bihemispheric cortical atrophy. Duplex ultrasound examination of the cervical vessels described small atherosclerotic plaques in the carotid bifurcations, with mixed echogenicity, without significant stenosis. The vertebral arteries were without stenotic lesions, with normal blood flow.

The electrocardiography and echocardiography that were performed, were normal.

We interpreted the case as an atherothrombotic ischemic stroke in the deep territory of right middle cerebral artery. The patient received appropriate antithrombotic treatment (acetylsalicylic acid 100mg in the first day, 100mg/day with Clopidogrel 75mg/day for 4 days, followed by Clopidogrel 75mg/day), statin, antihypertensive and antidiabetic treatment for secondary prevention. He also underwent neurorehabilitation, with favourable outcome. His modified Rankin Scale at discharge was 3 (ambulatory).

In March 2014, he presented in the neurology office with lancinating pain in his left sided upper and lower extremities, personality changes, emotional lability, insomnia. The patient lost 10 kg in the last 2 month. The neurological examination described left central facial palsy, grade 4 left hemiparesis, exaggerated deep tendon reflexes in the left lower limb, diminished left biceps and triceps reflexes, extensor plantar response on the left side, left hemihypoesthesia, atrophy in the small muscles of the left hand with wasting of left hypothenar eminence, vibration and position senses were not affected. The patient was admitted in the neurology ward for further investigations.

The psychiatric examination revealed: depression, emotional lability, anhedonia, micromania, slowed thinking, speaking and body movements, fixation hypomnesia, mini mental state examination- 27 points. The diagnosis was major depressive disorder and treatment with Sertraline 100mg/day was initiated.

Brain MRI revealed in T2 and Fluid Attenuated Inversion Recovery Sequences (FLAIR) a right thalamic lacunar infarction, moderate diffuse cortical atrophy. The CT scan of the chest, abdomen and pelvis, upper and lower gastrointestinal tract endoscopy excluded a neoplasm. The cervical spine MRI was without pathological changes.

Neurophysiological examination revealed normal motor and sensory conduction velocities. Needle electromyogram showed neurogenic changes with rich ongoing denervation activity and chronic partial reinnervation in several muscles, but more pronounced in the left upper limb.

Laboratory studies revealed positive Venereal Disease Research Laboratory (VDRL) serology and positive treponemal pallidum hemagglutination test index (TPHA). Complete blood count, erythrocyte sedimentation rate, serum chemistry, vitamin B12 level, FT4 and TSH were normal. Negative results were obtained for antinuclear antibodies, anti-dsDNA antibodies, cryoglobulin levels, lupus cells, HIV-1 and HIV-2 antibodies,

prostate-specific antigen (PSA), anti *Borrelia burgdorferi* antibodies, hepatitis B and C antibodies, and antigens in serum.

CSF analysis revealed elevated protein level (601 mg/l), lymphocytic pleocytosis (19 cells/microL, 99% lymphocytes), positive TPHA.

Based on clinical examination and laboratory tests, the diagnosis of neurosyphilis was established.

The patient denied having any signs of primary or secondary syphilis in the past. He reported having engaged in unprotected heterosexual activity several years previously, but the exact time of infection was not defined.

The treatment with high doses of Penicillin was initiated (24MU/day) 10 days followed by Ampicillin, because the patient developed an allergic reaction to Penicillin

The evolution was towards rapid aggravation of the symptoms, with progressive dementia, psychosis and general paresis. 2 weeks after the diagnosis the patient was bedridden, with significant psychical and physical disability, without improvement after antibiotics, vascular and psychiatric medication. The patient died 3 months after the diagnosis.

## DISCUSSIONS

NS was very common in the pre-antibiotic era, affecting about 35% of patients with syphilis. Of these, 30% had asymptomatic neurosyphilis, 30% had tabes dorsalis, at least 10 % had paresis, 10% meningovascular syphilis, the remaining patients having other forms of NS as symptomatic meningitis and cranial nerve palsies.(5,6)

Nowadays, early disease is more common than late form of syphilis and is more frequently seen in HIV patients.(7)

Our presented case illustrates that despite the fact that the incidence of NS in the general population is low, the classical cases are rare, the possibility of this disease cannot be neglected, and we must think about it even if the etiology of stroke seems to be clear. Sometimes, patients are unaware of the disease or tend to deny the existence of the disease in the medical history because of shame. Our patient had several risk factors for stroke as age, sex, hypertension, diabetes, atherosclerosis.

Also, the delimitation of the classical forms of NS is not already possible. Our case presented elements of meningovascular syphilis, general paralysis and syphilitic amyotrophy probably due to meningo-myelitis. Atypical forms of NS are not rare in the antibiotic era. The term is used for the forms that not fulfil the clinical criteria for one of the classical forms as asymptomatic NS, symptomatic meningitis, meningovascular syphilis, general paresis and tabes dorsalis.(8)

The form of meningovascular syphilis implies an infectious arteritis that may affect any vessel in the subarachnoid space around the brain and spinal cord and result in thrombosis, ischemia and infarction. This form can manifest as ischaemic stroke. The average interval for the onset of stroke from the infection is 7 years, but can range from the first months to several years. The middle cerebral artery and its branches are most commonly affected. The CSF abnormalities in this form usually consist in lymphocytic pleocytosis (10-100 cells) and elevated protein level.(3)

The late NS include the forms of general paresis and tabes dorsalis. The general paresis (paretic NS, dementia paralytica) involves progressive dementia. Usually, it develops 10-25 years after the infection and results in death within an average of 2.5 years. This stage usually begins with personality changes, mild cognitive impairment, followed by progressive worsening leading to severe dementia. Patient in this stage may develop depression, mania and psychosis. The neurological

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manifestations can be protean: from normal neurological examination to pupillary abnormalities (Argyll Robertson pupils), dysarthria, facial and limb hypotonia, tremor of the face, tongue, extremities and reflex abnormalities. In this stage of the disease the CSF abnormalities are always present (pleocytosis, elevated protein level, positive VDRL).

Tabes dorsalis is rare in the antibiotic era. Imply the affection of posterior columns of spinal cord and the dorsal roots. The latent period from the infection is the longest (about 20 years). The most important symptoms are the sensory ataxia and lancinating pain. Pupillary abnormalities are frequently found. The CSF can be normal in this form, or may reveal mild pleocytosis and elevated protein concentration. The VDRL can be negative.(3)

In our case, the origin of central pain was probably secondary to the thalamic lacunary infarction.

The term syphilitic amyotrophy is usually reserved for muscular atrophy which occurs in meningo-myelitis. It was first described by Ballet, in 1984, and the first case was published in 1910 by Mott. Amyotrophic meningomyelitis was described in detail by Martin, in 1925, based on clinical data from 60 cases.(9) They described a bilateral or unilateral atonic atrophy beginning in the small muscles of the hand, shoulder girdle or in legs, and often is preceded by pain.(10) Very few cases were reported since then.

El Alaoui-Faris M et al published 5 cases of syphilitic amyotrophy mimicking amyotrophic lateral sclerosis. Clinically, the disease affected the arms in 3 cases and produced paraplegia in 2 cases. The evolution was favorable after treatment with penicillin G in high doses, with improvement of motor deficit in 4 cases and stabilisation in 1 case in a 5 to 13 years' follow-up.(10)

The differential diagnosis of NS includes plexus lesions after vaccinations (our patient had no history of vaccination), neuroborreliosis (negative serology), cervical myelopathy, syringomyelia, vascular lesions or tumors (excluded radiologically), spinal muscular atrophy, toxic polyneuropathies, neuralgic amyotrophy.(11)

In the diagnosis of NS the clinical suspicion, serum and CSF analysis are essential. Nontreponemal (VDRL, RPR-rapid plasma reagin) and treponemal test (FTA-ABS - Fluorescent treponemal antibody absorption, TPHA-Treponema pallidum Haemagglutination Assay, EIA - syphilis enzyme immunoassay) are used. Diagnosis requires a combination of these tests. The CSF VDRL is the standard serological test, is highly specific but insensitive. A negative VDRL-CSF result does not rule out neurosyphilis. In addition to a reactive VDRL, diagnosis depends on reactive serological tests and CSF abnormalities. FTA-ABS is more sensitive than VDRL-CSF but less specific. Therefore, the CSF FTA-ABS test may be useful to exclude neurosyphilis. PCR-based tests have a high reliability.(12)

The standard treatment of the disease is high dose penicillin G. (18-24 MU/day) for 10-14 days. Alternative regimens are ceftriaxone, doxycycline, amoxicillin.(13,14)

The Jarisch-Herxheimer reaction (JHR) may complicate the therapy with high doses of intravenous penicillin. It is the result of massive lysis of the spirochetes, with the release of inflammatory cytokines into the bloodstream. JHR usually begins 1-2 hours after the initiation of penicillin and consists in fever, chills, myalgias, headache, hyperventilation, haemodynamic instability and exacerbation of skin lesions.(15)

it is rarely taken into account in the differential diagnosis.

Despite a dramatic decline in the incidence of NS since the early 20<sup>th</sup> century, the clinicians need to remain aware of the clinical presentation, diagnosis and treatment of NS because new cases are still occurring.

Patients presenting risk factors for venereal diseases and subtle neurologic or psychiatric symptoms should undergo a serologic screening with a specific treponemal test, and if positive, lumbar puncture for CSF-VDRL and cell count.

Syphilitic amyotrophy is still an existing differential diagnosis of progressive weakness of an amyotrophic limb.

## REFERENCES

1. Vedes E, Geraldo AF, Rodrigues R, et al. Neurosyphilis versus Herpes Encephalitis in a Patient with Confusion, Memory Loss, and T2-Weighted Mesiotemporal Hyperintensity. *Case Rep Infect Dis.* 2012;2012:154863. doi: 10.1155/2012/154863. Epub 2012 Feb 16.
2. Pearce JMS. Brain disease leading to mental illness: a concept initiated by the discovery of general paralysis of the insane. *Eur Neurol* 2012;67:272-278
3. Marra MC. Neurosyphilis. In: UpToDate, Dashe JF (Ed) UpToDate, Waltham, MA. (Accessed on August 17, 2014)
4. Hewitt AB. Syphilitic amyotrophy- a case occurring after apparently successful treatment in primary syphilis. *Brit J Vener Dis* 1967;43:272
5. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford; 1946.
6. Stokes JH, Beerman H, Ingraham NR. Modern Clinical Syphilology: Diagnosis, Treatment, Case Study. 3rd ed, Philadelphia: WB Saunders; 1944.
7. Taylor MM, Aynalem G, Olea LM, et al. A consequence of the syphilis epidemic among men who have sex with men (MSM): neurosyphilis in Los Angeles, 2001-2004. *Sex Transm Dis* 2008;35:430-434
8. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. *JAMA* 1972; 219:726.
9. Martin JP. Amyotrophic meningo-myelitis: spinal progressive muscular atrophy of syphilitic origin. *Brain* 1925;48 (2):153-182
10. El Alaoui-Faris M, Medejel A, al Zemmouri K, et al. Amyotrophic lateral sclerosis syndrome of syphilitic origin. 5 cases. *Rev Neurol Paris* 1990;146(1):41-4.
11. Etrgen T, Bischoff C, Resch M, et al. Obstacles in the diagnosis and treatment of syphilitic amyotrophy. *Neurology* 2003;60:509-511.
12. Ratnam S. The laboratory diagnosis of syphilis. *Can J Infect Dis Med Microbiol* 2005 Jan;16(1):45-51.
13. Yim CW, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob Agents Chemother* 1985;28:347.
14. Parkes R, Renton A, Meheus A, Laukamm-Josten U. Review of current evidence and comparison of guidelines for effective syphilis treatment in Europe. *Int J STD AIDS* 2004;15:73.
15. Mehrabian S, Raycheva MR, Petrova EP, et al. Neurosyphilis presenting with dementia, chronic chorioretinitis and adverse reactions to treatment: a case report. *Cases J.* 2009 Sep 1;2:8334. doi: 10.4076/1757-1626-2-8334.

## CONCLUSIONS

Syphilis is often described as "the great imitator" and our ability to correctly diagnose it is sometimes limited because