



The great imitator: How Neurosyphilis remains a diagnostic and therapeutic challenge in psychiatry - two case-reports

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Abstract

Although worldwide prevalence has decreased with the onset of antibiotic therapy, syphilis plays an important role in modern medical and psychiatric practice. Neurosyphilis, a Central Nervous System infection caused by the spirochete *Treponema pallidum*, is a serious pathology that leads to deterioration of the disease with a significant impact on his life and also on the caregivers'.

The authors propose a brief review of the topic based on the clinical cases of two patients admitted to sudden manifestations of cognitive and behavioral changes diagnosed with neurosyphilis, reflecting on the importance of the exclusion of organic causes and the treatment of psychiatric symptomatology. These events are usually diagnosed as rapidly progressive dementia, which may be due to different causes, so that the psychiatrist must assume a high degree of suspicion. Although there is a standard treatment with penicillin for neurosyphilis, in the current literature there is no evidence regarding the treatment of its psychiatric manifestations, although there is an apparent benefit in the judicious use of antipsychotics.

Keywords: Neurosyphilis, dementia, rapidly progressive dementia, behavioral change, antipsychotics

Introduction

A large number of autoimmune, infectious, endocrine, metabolic and neoplastic diseases are manifested through neuropsychiatric symptoms, so their correct identification can be crucial, since many conditions can be reversible with appropriate and timely treatment ^[1].

Syphilis is a disease that has plagued humans for over 500 years and in the pre-antibiotic era it is estimated that 25-30% of patients admitted to psychiatric facilities were positive for syphilis ^[2]. Although the worldwide prevalence has decreased with the appearance of penicillin antibiotics, syphilis maintains an important role in modern medical and psychiatric practice, and can present itself in four stages: primary syphilis, which occurs at the inoculation site, usually exhibiting a painless macula, which may ulcerate later; the secondary form, which often occurs 4-8 weeks after infection, manifesting itself in a generalized rash involving the palms and soles. At this stage, it is also possible to verify the concomitant presence of systemic vasculitis. If left untreated, approximately 30% of individuals develop the tertiary form of syphilis, essentially expressed through cardiovascular and neurosyphilis manifestations. These phases can be interspersed with the latent phase of the disease, usually asymptomatic ^[3]. Even after several years in the latent phase, the infection can re-manifest itself through sensory ataxia and intestinal/bladder dysfunction, a phenomenon called *Tabes dorsalis* or general paralysis. Although less frequent, it may also present in the form of rapidly progressive dementia ^[4].

Neurosyphilis represents an infection of the central nervous system caused by the spirochete *Treponema pallidum*. Also referred to as "The Great Imitator", it represents a disease with multiple symptomatic neurological and psychiatric presentations, including psychosis, changes in personality and behavior, depression, mania and dementia, which often leads to a wrong diagnostic identification. Thus, despite the increased incidence of the tertiary form of syphilis, associated with the increased prevalence of HIV co-infection, neurosyphilis remains an uncommon finding in immunocompetent individuals, so that in this population, its rapid diagnosis becomes challenging ^[5].

The authors seek to emphasize the importance of a timely suspicion of neurosyphilis, to the exclusion of other diagnoses that may mimic a rapidly progressive dementia, discussing the diagnosis and treatment of the disease, including the control of psychiatric symptoms.

Case Report #1

62-year-old man, unemployed, widowed, brought to the Emergency Department (ED) for an incoherent speech, centered on delusional ideas of prejudice and grandeur, accompanied by manifest behavioral disorganization with aggressiveness aimed at family members. Until then, he would be autonomous, with good socio-family relationships, with no history of previous psychiatric illness and a history of arterial hypertension, dyslipidemia and atrial fibrillation, with adequate medical

monitoring and treatment.

Upon admission, he presented temporal disorientation and high-speed speech, detailed and difficult to organize. It revealed persecutory and prejudice content towards neighbors, presenting various delusional interpretations in this context. Analytically, he showed a slight increase in C-reactive protein (CRP). Initially, the condition was interpreted as a possible manifestation of an incipient dementia. He was transferred to a psychiatric ward, where he remained hospitalized for 49 days, on a compulsory basis (under the Portuguese mental health law) due to the lack of insight.

On the sixth day of hospitalization, after an analytical study with a positive VDRL (Venereal Disease Research Laboratory), diagnostic exclusion of neurosyphilis was necessary, which could justify the disorientation and behavioral changes. After the serological diagnosis of neurosyphilis (VDRL positivity in cerebrospinal fluid (CSF)) was confirmed, intravenous treatment was started with sodium and potassium penicillins, administered alternately every 4 hours for 14 days. Additionally, risperidone 6mg/day was introduced.

Overall, there was a behavioral improvement of the patient, maintaining, however, periods of confusion, confabulatory speech centered on megalomaniacal delusional ideas, without detection of hallucinatory phenomena. At discharge date, he maintained residual delusional ideation, under therapy with risperidone 6mg/day, which he maintained during subsequent reassessments.

Case Report #2

60-year-old man, single, unemployed, admitted to the ED due to behavioral changes, heteroaggressiveness, psychomotor agitation and incoherent speech. He had a history of excessive alcohol consumption (60g/day) and tobacco, not undergoing any chronic therapy.

He presented spatio-temporal disorientation, dysphoric humor and disorganized speech, showing an apparently ill-structured persecutory delusional ideation. Dupuytren's contracture was detected bilaterally and analytically presented increased CRP and leukocyturia, with the diagnosis of confusional syndrome secondary to urinary infection being admitted, starting antibiotics with ceftriaxone. He performed a lumbar puncture that revealed pleocytosis with a predominance of lymphocytes and proteinorrhagia, taking a sample for microbiological study. Given the evolution over a week and the characteristics of the CSF, the hypothesis of viral meningoencephalitis was considered probable, starting treatment with acyclovir. He remained hospitalized for 20 days in a medical ward, showing positive for the VDRL in the CSF, starting intravenous treatment with penicillin. A Magnetic resonance imaging (MRI) was performed, which revealed multiple diffuse vascular lesions in white matter, suggestive of syphilis vasculopathy.

5 days after hospital discharge, he would return to the ED due to new contempt and aggression directed at family members. He had worsening inflammatory parameters and changes in kidney function, so he was admitted to a medical ward again with the diagnosis of acute kidney injury. Returning home, he maintained the behavioral changes previously described, so he was hospitalized on a compulsory basis in the Psychiatric ward for psychopathological stabilization, where he remained 61 days.

Psychopathologically, he presented a gradual behavioral stabilization with the introduction of risperidone 6mg/day, fading of delusional ideation, despite having a depressive mood (and emotional lability), with 15mg/day of mirtazapine. At discharge, he maintained the absence of structured delusional activity and hallucinatory phenomena, despite the absence of insight.

Discussion

The cases share symptomatology recurrently found in patients diagnosed with neurosyphilis, characterized by cognitive decline, behavioral change with periods of psychomotor agitation and which often sets in and evolves rapidly in just a few weeks or months. Observation of these characteristics should lead to the suspicion of rapidly progressive dementia. The differential diagnosis related to this nonspecific clinic must, in addition to neurosyphilis, include, among others, vascular/ischemic, infectious, toxic-metabolic, autoimmune, neoplastic and neurodegenerative causes [6].

The first case depicts a patient with a thromboembolic risk (atrial fibrillation), so it is important to exclude a vascular cause in the etiological explanation. In both cases, taking into account the probable food neglect and frequent alcohol consumption, hydroelectrolytic disorders and vitamin deficits must be ruled out. Thiamine deficiency can cause Wernicke's encephalopathy, characterized by ophthalmoparesis syndrome, ataxia and cognitive deterioration. Also taking into account age and smoking habits, neoplastic causes of dementia should always be excluded. Brain damage can occur in late syphilis, usually 18 to 25 years after primary infection, and usually under the form of rapidly progressive cognitive decline with spatio-temporal disorientation, delusional thinking, irritability, changes in sensory perception and personality, as well as dysarthria and limb tremors and paresis. Urinary and fecal incontinence, changes in sleep patterns and epileptic seizures are also common symptoms.⁷ In both cases, delusional persecutory ideation was found. Among the typical forms of neurosyphilis (85% of all cases), the schizophrenic form, although less frequent than the simple and manifest dementia forms, is characterized by a paranoid condition, with persecutory or grandiosity ideas, poorly systematized, and may be accompanied by hallucinations (visual or auditory) [8].

Its multiple forms of presentation make neurosyphilis one of the most difficult pathologies to diagnose in the absence of a previous history of syphilis infection. However, the presence of personality and speech disorders, hyperreflexia, Argyll-Robertson pupils and psychotic symptoms are strongly suggestive of this diagnosis. These symptoms are caused by progressive fronto-temporal meningoencephalitis with diffuse cortical atrophy [9]. *Tabes dorsalis*, caused by slow demyelination of the posterior columns of the spinal cord, can occur at any time and up to 50 years after infection, manifesting by excruciating pain and sensory ataxia [10]. Argyll-Robertson pupils - bilaterally small pupils - are a very specific finding of neurosyphilis, resulting from lesions of the cells in the midbrain's pretectal region, with the photomotor reflex compromised, keeping the accommodation reflex intact [11].

If symptoms occur early in the disease, the spirochete usually affects the CSF, meninges, and blood vessels. The late variant of the disease affects the cerebral parenchyma and spinal cord. CSF

analysis obtained through lumbar puncture is necessary in patients with syphilis and neurological symptoms, as well as in patients who maintain positive clinical or serology even after therapy is instituted [12].

The serologies for the detection of *T. pallidum* can undergo different treponemic tests, especially the FTA-ABs (indirect immunofluorescence test), TPHA (hemagglutination tests) or EIA (immunoenzymatic tests) and can be complemented with non-treponemic tests such as the VDRL, RPR (Rapid Test Reagin), USR (Unheated Serum Reagin) and TRUST (Toluidine Red Unheated Serum). The positivity of the VDRL in the CSF contributes to the diagnostic confirmation of neurosyphilis, although a negative result does not allow to exclude the disease, and the VDRL may be negative at the beginning of the infection (first 4-8 weeks) and in the late forms of the disease. TPHA and FTA-ABs, which are more specific and sensitive, are indicated mainly in cases of doubt regarding the VDRL result and in patients with late syphilis symptoms, in which non-treponemal tests can be negative [8].

Although electroencephalography does not present specific findings, it may reveal slow and arrhythmic brain activity, usually asymmetric, and with increased delta waves. Neurosyphilis neuroimaging is also non-specific and therefore has limited diagnostic value. The main changes seen in cerebral MRI include focal atrophy (mainly frontal and temporal), with bilateral enlargement of the ventricles [7]. Cerebral angiography is a useful diagnostic method to differentiate ischemia due to stroke from ischemia caused by cerebrovascular syphilis, which usually presents multifocal involvement of smaller caliber arterial branches, with a diffuse and irregular involvement of intracerebral arteries and arterioles.

In patients without penicillin allergy, the first line of treatment consists of aqueous crystalline penicillin G (3-4 million units IV 4/4 hours) for 10-14 days, or procaine penicillin (2.4 million units IM / day) together with probenecid (500 mg orally 4x / day) for 10-14 days [13]. The patient should be reevaluated with serologies for *T. Pallidum* and CSF analysis at 6, 12 and 24 months of follow-up.

The therapeutic outcome of the patient with neurosyphilis is highly dependent on the extent of the brain injury and the degree of disability prior to the start of treatment. Cognitive deficits and psychiatric symptoms, including psychotic symptoms and mood changes, are commonly associated with the tertiary form of the disease, so the use of antipsychotic drugs to control these symptoms has been practiced, although there are no therapeutic guidelines [13].

The treatment of psychiatric symptoms with haloperidol (10-20mg/day), risperidone (3-6mg/day) or quetiapine (300-800mg/day), demonstrated benefit in these presentations. The addition of anti-epileptic drugs and sodium valproate can be used to stabilize mood and agitation in some patients. Treatment should be continued for a period of 3 to 6 months before considering a decrease in dosage or discontinuation [13].

Given that cholinergic hypoactivity plays an important role in cognitive dysfunction due to systemic inflammation, the use of reversible acetylcholinesterase inhibitors such as donepezil (10mg/day) has proven to be effective when used concomitantly with penicillin therapy in some studies [14].

In patients allergic to penicillin, intravenous treatment with

ceftriaxone 2g/day for 14 days, or oral treatment with doxycycline 200mg 2x/day for 28 days also showed efficacy [13]. In patients with long QT interval, treatment of psychotic symptoms with aripiprazole 15mg/day, later replaced by the 400mg monthly intramuscular formulation, proved to be a good alternative [15].

Conclusion

These reports highlight the diagnostic (and therapeutic) challenge related to the great diversity of psychiatric symptoms that accompanies sudden cognitive-behavioral changes, especially in those with no previous psychopathological history. These events, often with only a few weeks of evolution, can be attributed to different causes, requiring a high degree of suspicion and the use of targeted complementary diagnostic tests.

Although there is a standard treatment with penicillin globally accepted for neurosyphilis, in the current literature there is a lack of evidence / agreement regarding the treatment of psychiatric manifestations, with an apparent benefit in the judicious use of antipsychotics.

Neurosyphilis is a serious condition that leads to the deterioration of the patient with a significant impact on his or her life and that of family members, so the later it is treated, the more severe the cognitive and behavioral sequelae presented. If left untreated, death usually occurs in 4-5 years.

Disclosure

The authors declare that they have no conflict of interest.

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