CASO CLÍNICO / *CLINICAL CASE*

Neurossífilis com apresentação meníngea aguda

Neurosyphilis presenting as acute meningitis

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/ Resumo

A neurossífilis define-se como a infecção do sistema nervoso central pelo *Treponema pallidum*, podendo ocorrer em qualquer fase da doença. Na era pré-penicilina, a doença era ubíqua e uma importante causa de morbilidade e mortalidade. Desde 2001 que se verifica o reaparecimento da sífilis, com elevada prevalência em indivíduos coinfetados pelo vírus da imunodeficiência humana. Apesar de a neurossífilis ser um diagnóstico incomum, a sua prevalência está a aumentar, frequentemente com manifestações atípicas.
Os autores apresentam um caso de um homem de 52 anos que recorreu ao serviço de urgência por um quadro agudo de meningismo: a história sexual evocou o diagnóstico de neurossífilis que foi confirmado com Venereal Disease Research Laboratories (VDRL) reativo no líquido céfalo-raquidiano.

Palavras-chave: Neurossífilis; Sífilis; Meningite; *Treponema pallidum*

/ Abstract

Neurosyphilis is defined as the infection of the central nervous system at any stage of the disease by **Treponema pallidum**. *In the pre-penicillin era the disease was ubiquitous and a major cause of disability and death. Since 2001 there has been a resurgence of syphilis, with high prevalence among individuals coinfected with human immunodeficiency virus. Although neurosyphilis is now uncommon, its prevalence may be increasing and often with atypical manifestations.*
Here we present a case of a 52-year-old male that presented in the emergency department with acute presentation of meningitis: the sexual history evoked the diagnosis of neurosyphilis that was confirmed with a reactive Venereal Disease Research Laboratories (VDRL) in the cerebrospinal fluid.

Keywords: *Neurosyphilis; Syphilis; Meningitis;* **Treponema pallidum**

/ Introduction

Treponema pallidum subspecies pallidum, the causative agent of syphilis, disseminates to the central nervous system within days after exposure[1]. Clinical manifestations can occur at any time in the course of the infection, thus, neurosyphilis should not be considered to be solely a "tertiary" manifestation of syphilis. The early forms of neurosyphilis occur within months to the first few years after primary infection and affect the meninges and blood vessels, while the late forms occur years to decades after primary infection and affect the brain parenchyma and spinal cord[2]. Early symptomatic neurosyphilis presenting as acute syphilitic meningitis was rare in the past and was rarely diagnosed in the pre-HIV era[3,4]. The majority of cases of acute syphilitic meningitis occurred after the inadequate treatment of early syphilis[2].

The diagnosis of neurosyphilis remains challenging because there are no standard criteria tests. Consequently, the diagnosis is based on clinical findings, the results of serologic tests and cerebrospinal fluid (CSF) examination.

/ Clinical case

A 52-year-old Caucasian male presented in the emergency department (ED) with an intense onset of headaches, confusion and behaviour changes. The patient complained of photophobia, nauseas and eye pain. He denied chills, vomit, seizures, other vision or auditory changes and no motor or sensory deficits. He also denied myalgias, diarrhoea, otorhinolaryngological and respiratory complaints.

He had history of arterial hypertension, diabetes mellitus and non-ST segment elevation myocardial infarction (NSTEMI) revascularized with a triple bypass 8 months before. He was medicated with ramipril 5mg, hydrochlorothiazide 25mg, pantoprazole 20mg, nifedipine 30mg, bisoprolol 2.5mg, metformin 1000mg twice a day, rosuvastatin 10mg, acetylsalicylic acid 150mg and clopidogrel 75mg. The patient consumed alcohol and did not smoke. He was heterosexual and reported multiples episodes of unprotected sex with unknown partners. During his twenties he recalls a penile lesion that was treated with one injection of intramuscular penicillin. By the time that he was hospitalized due to NSTEMI, he had VDRL reactive with a titer of 1:128 and *Treponema pallidum* hemagglutination assay (TPHA) reactive in the blood sample; latent syphilis of unknown duration was admitted and recommended treatment with one injection of penicillin 2.4 million units per week for three weeks. The patient only received one administration.

In the ED he was febrile (tympanic temperature of 38,1ºC), prostrated and disorientated. He was hemodynamically stable. He had no skin lesions and had no alterations in the cardiopulmonary auscultation. He had increased nuchal rigidity and a positive Kernig sign. He had symmetrical fall in both members in the Barré and Mingazzini tests. There was no facial asymmetry, oculomotor deficits or plantar extension response.

Analytically he showed leucocytosis 14.0x109/L, neutrophilia 83%, PCR 19 mg/dL. Renal and liver test function were normal. Urine sample was negative. Chest x ray was normal. HIV serology was negative. The brain computed tomography scan and electroencephalogram showed no relevant changes. The patient underwent lumbar puncture that was traumatic due to his agitation, the CSF showed numerous erythrocytes, 4900 leucocytes with polymorphonuclear predominance, a protein concentration of 453 mg/dL and a glucose concentration of 80 mg/dL (blood glucose 128 mg/dL.). He started empirical antibiotherapy with ceftriaxone, ampicillin and acyclovir.

In the third day after admission, the results from the ED showed serum Rapid Plasma Reagin (RPR) reactive with a titer of 1:128 and serum TPHA reactive; CSF-VDRL reactive with a titer of 1:8 and CSF-TPHA reactive. Blood and CSF cultures were negative. The bacterial capsular antigens to *Streptococcus pneumoniae*, Group B *Streptococcus*, *Neisseria meningitidis and Haemophilus influenzae type B* in CSF were not detected. Herpes simplex PCR in CSF was negative.

He stopped the empirical therapy and repeated lumbar puncture. The CSF was clear, showing 194 leucocytes with lymphocytic predominance, a protein concentration of 69 mg/dL and a reactive CSF-VDRL with a titer of 1:4.

The patient also received ophthalmologic examination which was negative.

Towards the clinical case and the findings of the CSF with pleocytosis and reactive VDRL, we assumed the diagnosis of neurosyphilis presenting as meningeal syphilis and he started treatment with intravenous benzylpenicillin sodium 4 million units every 4 hours for 14 days. The patient presented good evolution with complete resolution of the clinical symptoms. Seven months after the diagnosis of neurosyphilis, the patient was asymptomatic and repeated the lumbar puncture. The CSF was clear and showed resolution of pleocytosis and a non-reactive VDRL.

/ Discussion

Early neurosyphilis which manifests as meningeal or meningovascular involvement of the central nervous system was rare. However, in the beginning of AIDS epidemic, cases of neurosyphilis were noted in patients infected with human immunodeficiency virus. Particularly early neurosyphilis in patients who had been adequately treated for early syphilis; drawing attention to the possibility of increased risk of neurosyphilis in this population, and also reminding clinicians of a previously underrecognized disease[3].

Early symptomatic neurosyphilis involves diffuse inflammation of the meninges resulting in signs and symptoms of meningitis: Headache, stiff neck, photophobia, nausea, vomiting, cranial nerve palsies (including optic or auditory neuropathies manifesting as

blindness, vertigo and deafness), confusion, lethargy and occasionally seizures[2,3]. Syphilitic meningitis most commonly occurs within the first year of infection.

The described case reported a HIV negative patient presenting with typical findings of meningitis in which the CSF characteristics mimicked acute bacterial meningitis. The history of sexual risky behaviours had paramount importance for the suspicion of neurosyphilis together with the assessment of positive serology for syphilis, in the previous 8 months, with serum VDRL titer of 1:128 and reactive TPHA that was compatible with latent syphilis of unknow duration that was inadequately treated. In fact, according to literature most cases of acute syphilitic meningitis reportedly occurred after the inadequate treatment of early syphilis. In the pre-HIV and penicillin era, acute syphilitic meningitis was extremely rare suggesting that the combination of a robust immune system and an excellent drug (even a drug such as benzathine penicillin G that did not penetrate the CSF to achieve treponemicidal levels) was enough to control early CNS infection. The term "neurorecurrence" was coined after had been observed that most cases of acute syphilitic meningitis occurred after failed therapy of early syphilis[2]. The increased incidence in those who were inadequately treated suggest that inadequate or incomplete treatment may alter the immune response in such a way that increases the risk for early neurosyphilis[6].

Neurosyphilis has generally a white blood cell concentration in CSF greater than 10/mL with lymphocytic predominance. Pleocytosis although nonspecific, is a sensitive marker for neurosyphilis. Interestingly in the presented clinical case, the CSF showed, initially, marked pleocytosis (up to 2000 cells/mL that can be present in patients with acute meningeal syphilis)[2]; higher cell counts are seen in early compared to late neurosyphilis[3]. Also, polymorphonuclear lymphocytes may predominate especially in acute syphilis meningitis[2]. The CSF-VDRL test is very specific but a false-positive result may be seen when the CSF is visibly blood-tinged in patients with high serum VDRL[3]. The second lumbar puncture with clear CSF confirmed the VDRL reactivity with a titer of 1:4 and established the diagnosis of neurosyphilis. This lumbar puncture also showed pleocytosis with lymphocytic predominance. The CSF cell count appears to correlate with disease activity and is typically the first parameter to improve after therapy[6]. Finally, the follow-up lumbar puncture, 7 months after the diagnosis and treatment of neurosyphilis, demonstrated cure of the disease with resolution of the pleocytosis and non-reactive VDRL.

The diagnosis of neurosyphilis can be challenging, being essential recognizing the clinical manifestations and evaluating the advantages and pitfalls of the available diagnostic tests. Our case highlights the need to increase the suspicion of neurosyphilis in the broad differential diagnosis of acute meningism in at risk patients i.e. those with risky sexual behaviour. Promoting long term and adequate follow-up is essential in the management of these patients.

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