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ORIGINAL ARTICLE

NEUROSYPHILIS IN PATIENTS AT A UNIVERSITY HOSPITAL IN THE CENTRAL WEST REGION OF BRAZIL

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ABSTRACT

Syphilis remains a significant public health concern, and the central nervous system (CNS) involvement may occur at any stage of infection. Neurosyphilis must be ruled out in patients diagnosed with syphilis and exhibiting neurological or psychiatric symptoms, and cerebrospinal fluid (CSF) examination should be performed prior to treatment. A cohort of patients with neurosyphilis (aged ≥18 years old) was studied in a university hospital in the Central West Region of Brazil from 2018 to 2021. Twenty-four patients met the criteria for inclusion of confirmed neurosyphilis; 17 (70%) were male, with a median age of 37.5 (22–64). Six were asymptomatic, one had isolated otosyphilis, 11 had ocular syphilis, one had both ocular and otosyphilis, and five had other neurological symptoms. Thirteen patients (54%) were coinfected with HIV. Visual changes (50%) were the most common symptom; otosyphilis was present in 8.3%. Fourteen patients (58%) had positive VDRL in the CSF, and the median CSF-VDRL titer was 1:4. The cure rate was 87%, with three cases having persistent CSF-VDRL positivity after six months from the first treatment. In conclusion, understanding neurosyphilis, its clinical diversity, and its epidemiological and laboratory profile allows early diagnosis and treatment, consequently reducing its morbidity.

KEY WORDS: Syphilis; neurosyphilis; otosyphilis; ocular syphilis; HIV.

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INTRODUCTION

Syphilis is a systemic infection caused by the spirochete *Treponema pallidum*, exclusive to humans, which may progress to chronic illness (Radolf et al., 2020). Syphilis continues to be a significant public health concern with increasing prevalence worldwide. In 2021 Brazil had 167,523 notified cases of acquired syphilis, with a detection ratio of 78.5 cases/ 100,000 inhabitants, being 7.5% in the Central West region (Brasil, 2022a; Brasil, 2022b). Syphilis significantly increases the risk of infection with the human immunodeficiency virus (HIV), as the presence of syphilitic lesions facilitates HIV transmission (Garbin et al., 2019; Brasil, 2022a). Therefore, early recognition and prompt treatment are crucial to prevent irreversible damage and long-term sequelae.

Central nervous system (CNS) involvement may occur during any stage of syphilis, and laboratory abnormalities in the cerebrospinal fluid (CSF) are common among people with early syphilis, reaching 40% in secondary syphilis cases, even in the absence of clinical neurological findings (Caixeta et al., 2014). Therefore, neurosyphilis must be ruled out in those patients diagnosed with syphilis and exhibiting neurological or psychiatric symptoms (e.g., cognitive dysfunction, behavior changes, motor or sensory deficits, cranial nerve palsies, symptoms or signs of meningitis, or stroke). A CSF examination should be performed prior to treatment (Caixeta et al., 2014; Marra, 2015; Skalnaya et al., 2019).

Ocular syphilis may occur isolated or associated with additional CNS involvement, including CSF abnormalities in 10% to approximately 60% and a positive Venereal Diseases Research Laboratory (VDRL) in the CSF in up to 50% (Tuddenham et al., 2022). The symptoms of ocular syphilis may include decreased vision, redness, pain, photophobia, and floaters. Ocular findings usually include uveitis or optic neuritis, although other eye structures might be involved (Parc et al. 2007; Moradi et al., 2015).

Otosyphilis usually presents with cochleo-vestibular symptoms such as tinnitus, vertigo, or neurosensorial hearing loss. Hearing loss can start suddenly, unilateral or bilateral, quickly progressing to a permanent deficit (Yimtae et al., 2007; Workowski et al., 2021). Currently, there is no "gold standard" for diagnosing neurosyphilis; therefore, diagnosis is based on a combination of serological test results, clinical findings, CSF abnormalities, and neuroimaging (Marra, 2015; Skalnaya et al., 2019; Gaspar et al., 2021; Tuddenham et al., 2022;). This study aims to describe cases of neurosyphilis, including ocular and otosyphilis, treated at a teaching hospital.

MATERIAL AND METHODS

This is a clinical cohort of patients with confirmed neurosyphilis conducted in a tertiary teaching hospital in the Central West region of Brazil from 2018 to 2021. The outpatient infectious disease (ID) clinic attends mainly adult people living with HIV (PLHIV), patients previously hospitalized in the ID wards, and those referred by other specialties living or not with HIV. Semi-annual examinations are performed for monitoring patients with HIV, including clinical evaluation, routine laboratory exams, and quantitative VDRL testing, as recommended by the Brazilian Clinical and Therapeutic Guidelines (Brasil, 2022a).

Patients with syphilis whose VDRL did not show the expected decline throughout the treatment (two dilutions after six months of treatment), symptomatic or not, or patients with syphilis and the presence of neurological signs or symptoms were referred for an elective lumbar puncture (LP) and CSF collection for cytological, biochemical, microbiological, and VDRL analysis. A positive CSF VDRL result, regardless of the titer, or CSF abnormalities such as pleocytosis and/ or an elevated CSF protein level, without other causes to explain the CSF alteration, were considered as confirmed neurosyphilis cases (Xiao et al., 2017; Gaspar et al., 2021; Workowski et al., 2021; Brasil, 2022a).

Patients admitted to the infectious disease ward due to the positive serological tests (treponemal and non-treponemal) associated signs and/ or symptoms compatible with ocular and/ or otological impairment caused by the disease were also considered as confirmed cases. We excluded asymptomatic patients with normal laboratory CSF findings or another etiology that justified the clinical symptoms and laboratory abnormalities. All patients with confirmed neurosyphilis underwent cranial computed tomography (CT) or magnetic resonance imaging (MRI).

Patients who met the criteria for neurosyphilis underwent first-line therapy with intravenous crystalline penicillin G for 14 days. If penicillin was unavailable or the patient reported having a penicillin allergy, ceftriaxone for 14 days was prescribed instead. Treated patients underwent follow-up with blood VDRL testing every three months and a lumbar puncture with CSF examination 6-12 months after completing treatment.

Patients with adequate antibiotic use were considered satisfactorily treated if there was a drop in the blood VDRL titer of at least two dilutions, in addition to clearing the CSF abnormalities. We defined treatment failure or disease recurrence as cases with persistent or increased CSF VDRL titer 6-12 months after completing treatment (Workowski et al., 2021; Brasil, 2022a).

This study is in full accordance with the Brazilian legislation (Resolution 466/ 2012) and the declaration of Helsinki regarding ethical standards in conducting research involving human beings and it was approved by the ethical research committee (CAAE 6.096.360).

RESULTS

Sixty-five patients with suspected neurosyphilis, ocular syphilis, or otosyphilis were identified and underwent CSF collection and evaluation. Twenty-four patients met the inclusion criteria of confirmed neurosyphilis, of whom six were asymptomatic, one had isolated otosyphilis, 11 had ocular syphilis, one had both ocular and otosyphilis, and five had other neurological symptoms (Figure 1).

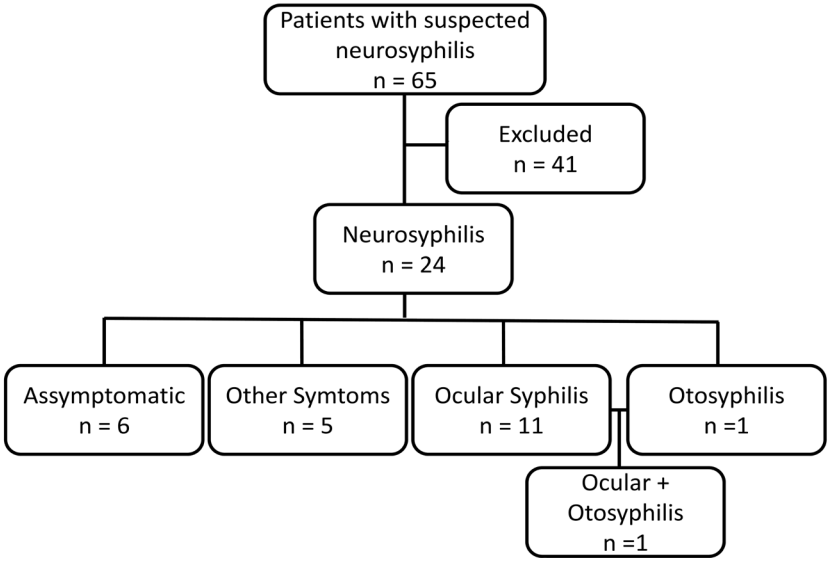

Figure 1. Flowchart describing the patients included in the study.

Of the 24 patients, 17 (70%) were male, with an average age of 37.5 years old (22–64 years old). Of 13 ocular and otosyphilis cases, seven (53%) were female, with 61% aged 40 years old or under. Thirteen (54%) were PLHIV, of whom three (23%) had a CD4 count <350 cells/μL and a detectable HIV viral load. The mean CD4 count was 497 cells/μL (19–968 cells/μL). Of 15 patients with sexual orientation data, 11 were heterosexual, one was bisexual, and three were men who have sex with men (MSM).

Fourteen patients (58%) had a positive VDRL in the cerebrospinal fluid (CSF-VDRL), and the median CSF-VDRL titer was 1:4. The nine asymptomatic individuals were HIV-positive men with undetectable viral loads and with a positive CSF-VDRL. Ten cases without a CSF-VDRL reactivity had ocular or otosyphilis, and eight patients (33%) had an initial CSF cellularity >10 cells/μL. The median CSF cellularity, glycorrhachia, and proteinorrachia are shown in Table.

Table. Clinical and demographic characteristics of 24 patients with neurosyphilis.

Variables	Patients (n = 24)
Gender (male) n (%)	17 (70.1)
Age (years) - mean (min-max)	37.5 (22–64 years)
Clinical forms n (%)	
Asymptomatic	06 (25.0)
Symptomatic	18 (75.0)
Symptomatic n (%) (May have more than one)	18 (100.0)
Otosyphilis	02 (8.3)
Ocular + Otosyphilis	01 (5.5)
Ocular Syphilis	12 (50.0)
Headache	04 (22.2)
Hemiparesis	01 (5.5)
Paresthesia	01 (5.5)
Cognitive impairment	01 (5.5)
HIV n (%)	13 (54.2)
LT CD4 - mean - cells/μL (range)	497 (19 – 968)
VDRL/blood - median (IQR)	1:64 (1:32 – 1:512)
CSF characteristic	
CSF-VDRL positive n (%)	14 (58.0)
CSF-VDRL - median (IQR)	1:4 (1:1 – 1:4)
Cellularity (cells/uL) – mean (range)	12.8 (0 – 145)
Proteinorrachia (mg/dL) – mean (range)	42.3 (22 – 77)
Glycorrachia (median)	57.64 (36 – 88)
Treatments	
Crystalline Penicillin G n (%)	21 (87.5)
Ceftriaxone	03 (12.5)
Relapse / Failure n (%)	03 (12.5)

n= number; range: minimum – maximum; IQR: interquartile range; LT CD4: CD4+ T lymphocyte count; CSF: cerebrospinal fluid

The common ocular and otological changes were uveitis, chorioretinitis, papilledema, hearing loss, and tinnitus. Five patients (21%) had other neurological symptoms besides ocular and otological, such as cognitive impairment, headache, paraesthesia, and paresis. Eight patients (33%) had normal cranial tomography or magnetic resonance imaging findings. The most common imaging abnormalities were hypodense parenchymal lesions or increased optic nerve thickness (Figure 2). Twenty-two of the 24 patients (87%) were considered cured. Three patients had a persistent positive CSF-VDRL in the follow-up examination and were considered failures or relapses, although re-exposition could not be ruled out. One patient was first treated with ceftriaxone and the other two with penicillin. They received a second treatment with an entire 14-day course of penicillin.

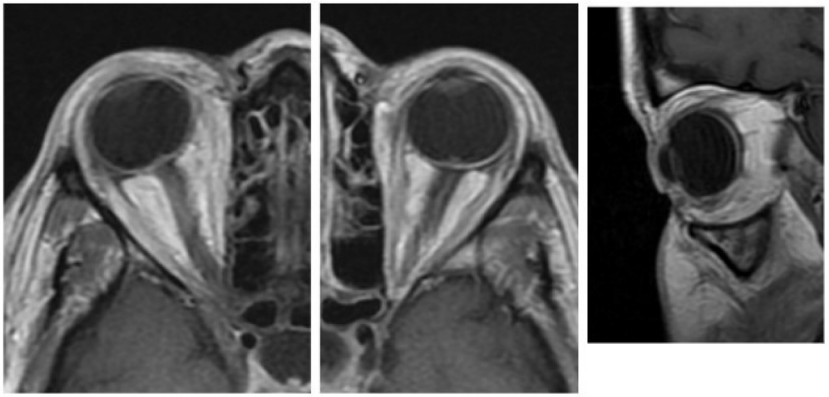

Figure 2. Patients with neurosyphilis experiencing panuveitis, as seen in the axial and sagittal post-contrast T1-weighted magnetic resonance imaging (MRI) scans. The scans reveal significant enhancement throughout the entire uveal.

The following two cases highlight the importance of conducting detailed clinical anamnesis and assessments, even in patients with only visual and auditive complaints. In addition, symptoms lasting longer than 30 days and the delayed diagnosis can have impacted some of the permanent sequelae. Therefore, healthcare professionals should have a heightened suspicion of neurosyphilis, especially as the incidence of the disease continues to rise in Brazil and globally.

Case 1

A single 25-year-old man attended the otorhinolaryngology outpatient clinic complaining of tinnitus for a month, followed by hearing loss in the left ear. He had a history of unprotected sexual intercourse in the previous six months, ulcers on the palate, and brownish spots on the palms of the hands and soles of the feet. Due to these complaints, he was investigated for syphilis, and his blood VDRL titer was 1:64. CSF analysis showed five leukocytes/uL, a predominance of lymphocytes, protein of 35 mg/dL, average glucose, and negative VDRL. The patient underwent cranial CT, which showed no changes. He received crystalline penicillin G for 14 days for otological syphilis treatment. During outpatient follow-up, he improved tinnitus, but follow-up audiometry showed persistent moderate sensorineural hearing loss. His blood VDRL titer decreased to 1:2 after six months.

Case 2

A single 23-year-old woman was referred to the infectious diseases department after consultation with the otorhinolaryngology team. She had experienced tinnitus and progressive bilateral hearing loss over the previous six months and she had developed blurred vision one month before. She reported unprotected sexual intercourse in the previous year. The blood VDRL was 1:128, and the CSF results showed 20 leukocytes/uL, with a predominance of lymphocytes, protein of 35 mg/dL, average glucose, and a negative CSF VDRL. Brain imaging showed no abnormalities. She had uveitis associated with otosyphilis and she was treated with crystalline penicillin G for 14 days. During outpatient follow-up, her blood VDRL titer decreased to 1:4, but her hearing loss and visual blurring had no improvement.

DISCUSSION

In our cohort, more than 50% of the patients were HIV positive, which may represent the characteristics of our tertiary center's ID clinic as a regional referral for PLHIV. Furthermore, according to the Brazilian Clinical and Therapeutic Guidelines, the prevalence of syphilis is higher in this population than in HIV-negative individuals, and this high rate is probably related to behavioral factors than to immunological factors (Radolf et al., 2020; Brasil, 2022a).

In addition, 70% of our patients were male, consistent with epidemiological data from the 2022 Brazilian Syphilis Report (Brasil, 2022b). From 2011 to 2022, there was a higher prevalence of syphilis among males (60.6%) when compared to women, with a sex ratio of 17 men for every 10 women. Furthermore, most notified syphilis cases occurred in the younger population aged 20-29 years old (35.6%) and 30-39 years old (22.3%), which is also in line with our findings (Brasil, 2022b).

In the absence of blood contamination, a reactive CSF-VDRL test is considered diagnostic of neurosyphilis for individuals who exhibit neurological signs or symptoms. However, it is important to note that while the test is highly specific, it may not be very sensitive (30-70%) (Gaspar et al., 2021). For example, in ten cases with negative CSF-VDRL, as the Centers for Disease Control and Prevention (CDC) Guidelines recommend, lymphocytic pleocytosis and elevated protein levels were considered to identify CSF involvement (Workowski et al., 2021).

People living with HIV might be at increased risk for neurologic complications and have higher rates of inadequate serologic response with recommended regimens (Workowski et al., 2021). A CDC (2007) study estimated the risk of having symptomatic early neurosyphilis in HIV-positive MSM at 1.7%. The six asymptomatic individuals with positive CSF-VDRL tests were HIV-positive men with no significant drop in VDRL titers. This supports the current recommendation to consider performing a CSF examination in asymptomatic people without two dilutions drop in nontreponemal titers, especially PLHIV (Marra et al., 2015; Tuddenham et al., 2022).

The cases of uveitis and otosyphilis were in younger patients, seven without factors associated with immunosuppression but with a history of unprotected sexual exposure. We detailed two cases of otosyphilis, as this condition is underreported in the medical literature (Witt et al., 2022). They exemplify the clinical features and radiological findings of a very specific type of neurosyphilis. These case reports add relevance to the study, understanding how early suspicion and diagnosis of otosyphilis can reduce unfavorable outcomes that can seriously impact the quality of life of affected patients.

Syphilis is a complex, multifaceted disease with the ability to affect multiple organs and systems and has both exuberant and silent clinical presentations, making diagnosis and treatment of neurosyphilis challenging (Tuddenham et al., 2022). Understanding neurosyphilis, its clinical diversity, and epidemiological and laboratory profile allows early diagnosis and treatment, consequently reducing its morbidity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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