Case Report

Oral doxycycline as an alternative treatment for early neurosyphilis in a patient living with HIV

Doxiciclina oral como alternativa de tratamento para neurossífilis precoce em um paciente vivendo com HIV

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ABSTRACT

This report aims to describe the successful treatment using oral doxycycline for early neurosyphilis in a patient living with HIV, primarily presenting with skin lesions. The therapeutic proposal, chosen by the patient and based on UK medical guidelines, has not yet been validated by the Brazilian Ministry of Health. The treatment consisted of a single dose of penicillin G benzathine (2.4 million units) administered intramuscularly, followed by oral doxycycline (200 mg twice a day) for 28 days, with quarterly outpatient follow-up. The patient's symptoms resolved on the first visit, and the nontreponemal test (VDRL) in the cerebrospinal fluid was negative after 6 months. The current literature offers inconclusive results; however, this case suggests that oral doxycycline is a safe alternative for treating neurosyphilis in select cases, especially for patients with penicillin allergies, while providing the advantage of avoiding hospitalization.

Headings: Neurosyphilis; HIV infections; Doxycycline; Case report.

RESUMO

Este relato visa reportar um tratamento bem sucedido de neurossífilis precoce com doxicilina oral prescrita a um paciente vivendo com HIV, sendo que sua queixa principal foi o aparecimento de lesões na pele. Além de ter sido esta a opção do próprio paciente, a proposta terapêutica baseou-se em diretrizes médicas adotadas no Reino Unido que, todavia, ainda não possuem validação pelo Ministério da Saúde no Brasil. O tratamento consistiu na administração de uma dose única de penicilina G benzatina (2,4 milhões de unidades) por via intramuscular, seguida de doxiciclina oral (200mg duas vezes ao dia) por 28 dias, com acompanhamento ambulatorial trimestral. O paciente evoluiu com resolução do quadro sintomático logo na primeira consulta e a negativação liquórica do teste não treponêmico (VDRL) depois de seis meses. Apesar dos resultados na literatura ainda não serem definitivos, este caso nos induz a uma reflexão sobre a doxiciclina oral como alternativa segura para o tratamento da neurossífilis em casos selecionados, seja por motivo alérgico às penicilinas ou pela vantagem de se evitar uma internação hospitalar.

Descritores: Neurossífilis; Coinfecção pelo HIV; Doxiciclina; Relato de Caso.

INTRODUCTION

Syphilis can be congenital or acquired, with the latter being divided into early or late[1]. These criteria are established based on the time elapsed between acquiring the infection and clinical manifestation or the detection of a reactive serological test result. Early syphilis includes the early latent (up to 1 year in duration, usually asymptomatic) and primary and secondary forms (progression of the primary infection). Late syphilis includes the late latent (lasting more than a year), tertiary forms and neurosyphilis[1]. Persistence of the infection in the central nervous system (CNS) leads

to syphilitic meningitis, with early neurosyphilis defined as CNS involvement up to 2 years after primary infection[2,3].

All patients with a reactive venereal disease research laboratory (VDRL) test in cerebrospinal fluid (CSF) should be treated for neurosyphilis, regardless of clinical signs or symptoms[4]. Other biochemical alterations in the CSF (even with a nonreactive VDRL test) and the concomitant presence of neurological, ocular, or otological signs and symptoms, or radiologic imaging characteristic of the disease in the CNS also warrant treatment[4-6].

There is a higher incidence of neurosyphilis among people living with human immunodeficiency virus (PLHIV), and patients with a CD4 cell count of less than 350/mm^3 are three times more likely to have neurological involvement[3]. However, the diagnosis of neurosyphilis in this group of patients is more challenging and controversial. European guidelines, for example, indicate that lumbar puncture should be performed on all PLHIV with late syphilis and a CD4+ count of ≤350 cells/mm^3 (including those without neurological signs and symptoms) and/or those with a serum VDRL titer greater than 1:32 in the event of therapeutic failure after treatment for late syphilis[5].

For all patients (including PLHIV) and clinical forms, syphilis treatment with penicillin is well established, with oral doxycycline emerging as an alternative option for the treatment of early and late syphilis, including in Brazil[6]. However, there are no data on the use of doxycycline in neurosyphilis in either the American[7], European[5], or Brazilian[6] guidelines. The official recommendation for the treatment of neurosyphilis is intravenous crystalline penicillin G (3–4 million units every 4 hours or by continuous infusion for 14 days), and ceftriaxone (2 g a day for 10–14 days) is presented as the only alternative to penicillin in these three guidelines. The official UK guidelines[8] are an exception in that they also include doxycycline as an alternative to parenteral penicillin for the specific treatment of neurosyphilis. Although this therapeutic option is not standardized in our country, it was used in the case reported herein, exemplifying a successful regimen of oral doxycycline in PLHIV with early neurosyphilis.

CASE REPORT

The patient was a 39-year-old heterosexual male from the interior of the state of Rio Grande do Sul, who had been living with HIV for 13 years. The consultation was prompted by the appearance of skin lesions 10 days before presentation, but he had been experiencing nausea and vomiting after meals for 30 days (for intermittent periods of 1–3 days), accompanied by dizziness, amaurosis, hand paresthesia, and an isolated episode of syncope. Ten days ago, erythematous spots appeared on his torso and progressed to his limbs, leading him to seek initial care at a basic health unit. There, he underwent a blood test that was positive for syphilis (VDRL titration of 1/16), a diagnosis that he linked to sexual exposure in a recent extramarital relationship. He had histories of anxiety and migraines as well as epilepsy as a result of a cryptococcoma diagnosed approximately 10 years ago. He was taking carbamazepine (200 mg three times a day), phenytoin (100 mg twice a day), escitalopram (10 mg twice a day), antiretroviral therapy for HIV (tenofovir 300 mg, lamivudine 300 mg, and dolutegravir 100 mg, the latter at a double dose due to the use of anticonvulsants), and fluconazole (150 mg three times a day) that was maintained continuously due to the recurrence of cryptococcosis after a previous attempt to discontinue the antifungal. The patient reported good adherence to treatment and outpatient appointments and progressed with a persistently undetectable HIV viral load and a last reported CD4+ cell count of 666/mm^3. It was decided to prescribe penicillin G benzathine (a single intramuscular dose of 2.4 million units) and advise the patient to seek specialist assessment at the tertiary referral hospital where he was routinely monitored for his underlying disease. This consultation took place 5 days later, and the patient had new complaints during that time, such as odynophagia and lumbar pain radiating to the trapezius muscles. He did not report fever, weight loss, or night sweats. On admission, he had erythematous, nonsquamous lesions on the trunk, abdomen, back, and medial region of the forearms, bilaterally. The remaining physical examinations showed no noteworthy alterations. His recent medical records included positive IgG results for toxoplasmosis and cytomegalovirus as well as nonreactive serologies for hepatitis B and C, Chagas disease, and HTLV. There was also a nonreactive VDRL test taken at the last visit, 4 months ago.

The patient underwent lumbar puncture for CSF collection, and the analysis showed normocellularity (5 cells), hypoglycorrhachia (64 mg/dL), normal proteinorrhachia (40 mg/dL), and VDRL reactivity (1/16). Based on this result, treatment for neurosyphilis with crystalline penicillin was indicated, but the patient refused hospitalization. The alternative treatment of ceftriaxone at a dose of 2 g/day was also declined, as it was deemed unfeasible to access in the patient's city of origin. By mutual agreement between the medical team and patient, it was finally decided to prescribe oral doxycycline 200 mg twice a day for 28 days.

After a month of treatment, the patient returned for an outpatient visit reporting the disappearance of the spots on his skin and the complete resolution of his back pain, denying any other neurological, ocular, or otological signs or symptoms during the period. He returned after 3 months and remained asymptomatic. On this occasion, the control serum VDRL titration was 1/4 (a drop of two dilutions compared to the pretreatment test result). A new CSF sample was taken at the third appointment - 6 months after treatment - and the VDRL result was negative. He therefore returned to his regular consultations every 6 months due to his HIV infection. Table 1 summarizes the serum and CSF VDRL results over the period.

DISCUSSION

All PLHIV diagnosed with syphilis should be assessed neurologically, and lumbar puncture is mandatory in the presence of neurological, ocular, or otological signs and symptoms[5,6,8,9]. In addition to its diagnostic importance, the nontreponemal VDRL test in the CSF serves as an important post-treatment monitoring indicator because a decrease in its titration is a sign of therapeutic success: a decline in the VDRL titration in the CSF greater than or equal to 4 times the initial value is expected 6–12 months after treatment for early neurosyphilis[9,10]. Normalization of serum VDRL levels combined with clinical response is also considered indicative of successful treatment of neurosyphilis[7] because this blood result usually predicts normalization of the VDRL result in the CSF, especially in PLHIV undergoing antiretroviral therapy (as occurred in this case). However, some studies showed that this drop in titration was not observed in certain patients, especially elderly and female patients[7,11].

The standard treatment for syphilis depends on the disease stage, while penicillin is used in almost all cases. *Treponema pallidum* is extremely susceptible to this antimicrobial due to its ability to block cell wall synthesis. Even after more than 60 years of clinical use, resistance has never been documented[12]. However, in some clinical situations (especially in allergic patients or in the event of a shortage)[13], it is necessary to opt for alternatives to penicillin treatment. Most studies on this topic are small, uncontrolled, and retrospective, with tetracyclines being notable for their pharmacokinetic properties and greater bioavailability (more specifically doxycycline at a dose of 200 mg twice a day)[5-7,9].

For neurosyphilis treatment, the primary objective is to ensure adequate antibiotic penetration across the blood–brain barrier. This requirement led to the use of crystalline penicillin instead of benzathine penicillin, which is typically used for other clinical forms of syphilis[5-7,14]. As an alternative or substitute, there is more robust evidence on ceftriaxone, which has been demonstrated to have an efficacy similar to penicillin G[14]. Meanwhile, the possibility of alternative oral treatment is particularly interesting and advantageous for neurosyphilis because both penicillin and ceftriaxone treatments require hospital care, which is not always available[8,10].

Sufficient evidence supports the efficacy of doxycycline as a suitable alternative for treating early and latent neurosyphilis[11]. This has therefore been one of the official recommendations in the UK since 2015, as long as the patient is properly monitored through outpatient appointments at least every 3 months, including a re-evaluation of the CSF at the end of 6 months of treatment[8]. In PLHIV, oral doxycycline may also be advantageous by reducing the risks associated with hospitalization, which can be elevated depending on the patient's degree of immunodepression[4].

Finally, it is worth noting that our patient received both an initial dose of benzathine penicillin and an additional 28-day course of oral doxycycline. Importantly, his main complaint was skin lesions, and benzathine penicillin is, by definition, the therapeutic recommendation for this secondary form of early syphilis. However, it was prescribed before the diagnosis of neurosyphilis; otherwise, the concomitant use of both treatments would not have been indicated. Conversely, considering that benzathine penicillin does not cross the blood–brain barrier, this double treatment cannot be considered a bias against the positive results obtained with doxycycline for the treatment of neurosyphilis, which is the main objective of this report[15,16].

Table 1. Evalution of the VDRL nontreponemal test results and its titers in blood and cerebrospinal fluid.

VDRL	Pre-admission (120 days before)	Admission	90 days	180 days
Blood	negative	positive (1/16)	positive (1/4)	positive (1/8)
CSF	not performed	positive (1/16)	not performed	negative

CONCLUSION

Oral doxycycline is not yet considered a validated option for the treatment of neurosyphilis in Brazil. Parenteral ceftriaxone is the only official alternative to penicillin; however, it's use necessitates either a hospital stay or daily visits to a healthcare facility for administration.

This report of a successful case of treatment of neurosyphilis with doxycycline highlights the need for further studies into the efficacy and safety of this drug in the long term and confirms its practicality because it does not require the patient to be hospitalized.

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