International Journal of Medical Science and Pharmaceutical Research

ISSN(e): 3050-5720
ISSN(p): 3050-5712

Vol. 3 (8): 414-422, August 2026

Home Page: https://ijmspr.org/

Successful Outpatient Management of Neurosyphilis with Benzathine Penicillin Plus Doxycycline: A Case-Based Review

Jozelio Freire de Carvalho, MD, PhD[1], Marjorie Vieira Batista, MD, PhD[2]

[1]Institute of Health Sciences, Federal University of Bahia, Salvador, Bahia, Brazil

[2]Department of Infectious Diseases and Infection Control, A.C. Camargo Cancer Center, São Paulo, SP, Brazil.

KEYWORDS:

Neurosyphilis, doxycycline, benzathine penicillin, case-based review, *Treponema pallidum*.

Corresponding Author:
Dr. Jozelio Freire de Carvalho

DOI: 10.55677/IJMSPR/2026-3050-I805

Published: August 21, 2026

ABSTRACT

Background: Neurosyphilis remains a major diagnostic challenge because of its heterogeneous neurological manifestations and the limited evidence supporting alternatives to guideline-recommended intravenous penicillin G. Doxycycline-containing regimens have been reported only sporadically, and their role in neurosyphilis remains poorly defined. We present a successfully treated case of neurosyphilis managed with benzathine penicillin plus doxycycline and performed a case-based review of the published literature.

Methods: A retrospective clinical review of the present case was conducted according to the CARE guidelines [10]. In addition, a comprehensive literature review was performed using PubMed/MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, LILACS, SciELO, and Google Scholar from database inception through July 2026 to identify reports describing doxycycline-containing regimens for neurosyphilis. Clinical characteristics, treatment strategies, and outcomes were extracted and qualitatively synthesized.

Results: An 81-year-old man presented with a one-month history of progressive dizziness, gait ataxia, pathological nystagmus, and a positive Romberg sign. Brain computed tomography demonstrated a right parietal extra-axial lesion suggestive of a subdural collection. Serum VDRL was reactive (1:64), FTA-ABS was positive, and investigations for HIV and other infectious diseases were negative. After refusing lumbar puncture and hospitalization, he received outpatient treatment with intramuscular benzathine penicillin (2.4 million units weekly for three weeks) plus doxycycline (100 mg twice daily for 28 days), achieving complete neurological recovery, radiological resolution, and progressive VDRL negativization during follow-up. The literature review identified only a limited number of reports, comprising isolated case reports and one retrospective cohort, indicating favorable outcomes with doxycycline-containing regimens in carefully selected patients but no high-quality comparative evidence.

Conclusions: Evidence supporting doxycycline for neurosyphilis remains scarce and is limited to low-level observational data. This case, together with the available literature, suggests that doxycycline-containing outpatient regimens may represent a reasonable individualized alternative when standard intravenous therapy cannot be administered. Nevertheless, intravenous penicillin G remains the recommended first-line treatment, and prospective studies are required to define the efficacy and safety of alternative therapeutic strategies.

Cite the Article: *Carvalho, J.F., Batista, M.V. (2026). Successful Outpatient Management of Neurosyphilis with Benzathine Penicillin Plus Doxycycline: A Case-Based Review. International Journal of Medical Science and Pharmaceutical Research, 3(8), 414-422. https://doi.org/10.55677/IJMSPR/2026-3050-I805*

INTRODUCTION

Neurosyphilis is a severe manifestation of *Treponema pallidum* infection that may occur at any stage of syphilis and can involve the meninges, cerebral vasculature, brain parenchyma, spinal cord, or cranial nerves. Although its incidence declined substantially following the widespread use of penicillin, neurosyphilis has re-emerged over recent decades in parallel with the global resurgence of syphilis [1].

Current international guidelines recommend intravenous aqueous penicillin G for 10–14 days as the standard treatment for neurosyphilis because of its established penetration into the central nervous system and extensive clinical experience [2–4]. The clinical spectrum is remarkably heterogeneous, ranging from asymptomatic cerebrospinal fluid abnormalities to meningitis, meningovascular disease, stroke, cognitive impairment, psychiatric manifestations, tabes dorsalis, optic neuropathy, hearing loss, and cerebellar dysfunction. This broad range of presentations frequently delays diagnosis and may mimic numerous neurological disorders [5,6].

The diagnosis of neurosyphilis remains challenging because no single laboratory or cerebrospinal fluid test demonstrates sufficient sensitivity and specificity to confirm or exclude the diagnosis in every clinical scenario. Consequently, diagnosis requires integration of neurological manifestations, serum and cerebrospinal fluid serological findings, neuroimaging, and exclusion of alternative neurological disorders [7,8].

Alternative regimens, including ceftriaxone, have been proposed for selected patients, whereas evidence supporting oral doxycycline remains limited to isolated case reports and small observational series. Pharmacokinetic studies have demonstrated that doxycycline achieves measurable concentrations in the cerebrospinal fluid, providing a biological rationale for its investigation as an alternative therapeutic option, although robust clinical evidence remains lacking [9]. Consequently, the role of doxycycline in the treatment of neurosyphilis remains uncertain, and data regarding combination regimens are exceedingly scarce.

Management becomes particularly challenging when hospitalization or intravenous therapy is not feasible because of patient refusal, limited healthcare resources, or other clinical circumstances. In these situations, physicians may be required to individualize treatment despite the lack of robust evidence supporting non-standard therapeutic approaches. Reports describing successful alternative regimens are therefore valuable, as they expand the available clinical experience while acknowledging that intravenous penicillin G remains the recommended first-line therapy.

We report the case of an elderly man who presented with progressive cerebellar dysfunction, reactive syphilis serology, and neuroimaging abnormalities consistent with central nervous system involvement. Because the patient declined hospitalization and intravenous penicillin therapy, he was treated in the outpatient setting with benzathine penicillin combined with doxycycline, resulting in complete clinical recovery, resolution of the neuroimaging abnormalities, and progressive serological normalization. We also review the available literature regarding doxycycline-containing regimens for neurosyphilis and discuss the potential role of individualized therapeutic strategies in carefully selected patients when standard intravenous treatment cannot be administered.

METHODS

Case report

This manuscript was prepared in accordance with the CARE (CAse REport) guidelines [10]. Clinical information was reconstructed from the contemporaneous medical records maintained by the treating physician and supplemented by the physician's direct recollection of the patient's clinical course. The case involved an elderly man who developed progressive neurological manifestations consistent with central nervous system involvement by syphilis. Demographic characteristics, medical history, neurological findings, laboratory investigations, neuroimaging, therapeutic intervention, clinical evolution, radiological follow-up, and serial serological responses were reviewed and summarized.

The diagnosis of neurosyphilis was established on the basis of a compatible neurological syndrome, reactive treponemal and non-treponemal serological tests, neuroimaging abnormalities, exclusion of alternative etiologies, and subsequent clinical, radiological, and serological response following antisyphilitic therapy. Cerebrospinal fluid examination was recommended but declined by the patient after discussion of its diagnostic value.

Written informed consent for publication could not be obtained because the patient is deceased. All potentially identifiable information has been removed to preserve confidentiality, and the manuscript was prepared in accordance with the ethical principles of the Declaration of Helsinki. According to local institutional requirements, formal ethics committee approval was not required for the publication of a single anonymized retrospective case report.

Literature review

To contextualize the present case, a comprehensive literature review was performed to identify published reports describing the use of doxycycline-containing regimens for the treatment of neurosyphilis.

Electronic searches were conducted in PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus, Cochrane Library, LILACS, SciELO, Google Scholar, and OpenGrey (when available), from database inception through July 2026. Reference lists of all eligible articles and relevant review papers were manually screened to identify additional publications. Grey literature, conference abstracts, and non-indexed reports were also considered when sufficient clinical information was available.

The search strategy combined controlled vocabulary and free-text terms related to neurosyphilis and doxycycline, including combinations of: "neurosyphilis", "Treponema pallidum", "doxycycline", "oral doxycycline", "benzathine penicillin", "benzylpenicillin", "penicillin G", "ceftriaxone", "alternative treatment", "case report", and "case series". Equivalent search terms were adapted for each database.

Eligible publications included case reports, case series, observational studies, and other original clinical reports describing patients with neurosyphilis treated with doxycycline either as monotherapy or in combination with other antimicrobial agents. Narrative reviews, editorials, expert opinions without original patient data, animal studies, and purely microbiological or pharmacokinetic investigations without clinical outcomes were excluded.

Two reviewers independently screened titles and abstracts, assessed full-text eligibility, and extracted data using a standardized form. Disagreements were resolved by consensus. Extracted variables included patient demographics, HIV status, neurological presentation, cerebrospinal fluid findings, neuroimaging characteristics, antimicrobial regimen, treatment duration, clinical response, radiological evolution, serological follow-up, cerebrospinal fluid response when available, adverse events, and duration of follow-up.

Given the anticipated clinical heterogeneity and the expected predominance of individual case reports and small case series, no quantitative synthesis was planned. Findings were synthesized descriptively to compare the present case with previously published evidence and to identify recurring clinical patterns, therapeutic approaches, and outcomes.

CASE PRESENTATION

An 81-year-old previously independent Brazilian man, a retired military officer, presented with a one-month history of progressively worsening dizziness, gait instability, imbalance, and recurrent near-falls. His medical history was notable only for well-controlled arterial hypertension treated with losartan. He also had longstanding bilateral sensorineural hearing loss secondary to chronic occupational firearm noise exposure during military service without hearing protection. He had no history of diabetes mellitus, immunodeficiency, previous neurological disease, head trauma, alcohol abuse, or tobacco use.

Neurological symptoms developed insidiously over approximately four weeks and progressively interfered with ambulation. The patient denied headache, fever, nausea, vomiting, diplopia, seizures, altered mental status, cognitive decline, urinary incontinence, focal weakness, sensory abnormalities, or constitutional symptoms.

Neurological examination demonstrated spontaneous pathological nystagmus, marked gait ataxia, impaired postural stability with a positive Romberg sign, and significant disequilibrium during walking. Motor strength, sensory examination, deep tendon reflexes, and cranial nerve examination were otherwise unremarkable except for the previously established bilateral hearing impairment.

Routine laboratory investigations demonstrated mild leukocytosis and a slight elevation of C-reactive protein, whereas renal and liver function tests were within normal limits. Serological testing revealed a reactive Venereal Disease Research Laboratory (VDRL) test with a serum titer of 1:64 and a positive fluorescent treponemal antibody absorption (FTA-ABS) assay. Serological investigations for HIV, hepatitis B virus, hepatitis C virus, HTLV, *Trypanosoma cruzi*, cytomegalovirus, Epstein–Barr virus, infectious mononucleosis, and other investigated infectious diseases were negative, and no alternative diagnosis explaining the neurological syndrome was identified.

Non-contrast brain computed tomography demonstrated a small right parietal extra-axial collection compatible with a chronic subdural collection in the absence of previous head trauma. The lesion was located in the right parietal to parieto-occipital convexity and was considered inconsistent with traumatic hemorrhage because of the absence of any precipitating injury and the concurrent evidence of active syphilitic infection.

Because of the neurological manifestations associated with reactive treponemal and non-treponemal serology, neurosyphilis was considered the most likely diagnosis. Cerebrospinal fluid examination was recommended but declined by the patient despite detailed counseling regarding its diagnostic value. Likewise, hospitalization for guideline-recommended intravenous aqueous penicillin G therapy was refused because the patient preferred outpatient treatment.

After reviewing the limited literature available at that time regarding doxycycline use in neurosyphilis, an individualized outpatient regimen was initiated consisting of intramuscular benzathine penicillin (2.4 million units administered weekly for three consecutive weeks) combined with oral doxycycline (100 mg twice daily for 28 days). The treatment was completed without adverse events.

Clinical improvement became evident during therapy, with progressive resolution of dizziness and restoration of normal gait and balance. Follow-up brain computed tomography demonstrated complete resolution of the previously observed extra-axial lesion. Serial serological follow-up at 3, 6, 9, and 12 months demonstrated a progressive decline in serum VDRL titers from 1:64 at diagnosis to 1:32, then 1:16, followed by complete serological negativization at approximately 9 months, which persisted at 12 months. As expected, the treponemal FTA-ABS remained positive throughout follow-up. No recurrence of neurological symptoms was observed during long-term clinical surveillance.

LITERATURE REVIEW

A systematic review of the literature identified an extremely limited body of evidence regarding the use of doxycycline-containing regimens for the treatment of neurosyphilis. Available data consisted primarily of isolated case reports and a single retrospective observational cohort, with no randomized clinical trials or prospective comparative studies evaluating doxycycline as definitive therapy for neurosyphilis [11–13]. Overall, the evidence remains based on low-level clinical data despite increasing interest in oral alternatives to prolonged parenteral therapy. The characteristics of all eligible studies are summarized in Table 1.

The earliest published experience was reported by Kang-Birken et al. in 2010, who described two HIV-infected patients with asymptomatic neurosyphilis successfully treated with high-dose oral doxycycline (200 mg twice daily for 28 days). Both patients demonstrated marked reductions in cerebrospinal fluid inflammatory parameters together with substantial declines in serum VDRL titers during follow-up, suggesting that adequate cerebrospinal fluid penetration of doxycycline may be sufficient to achieve microbiological control in selected patients. However, the small sample size and exclusive inclusion of HIV-positive individuals precluded any definitive conclusions regarding efficacy or generalizability [11].

The largest available clinical experience was subsequently reported by Girometti et al., who retrospectively evaluated 87 patients with early neurosyphilis, including 16 treated with oral doxycycline because of penicillin allergy, inability to attend daily parenteral therapy, physician preference, or patient refusal of intramuscular treatment. Clinical resolution was observed in virtually all patients, and all individuals receiving doxycycline achieved an appropriate serological response without significant differences compared with those treated using procaine penicillin-based regimens. Nevertheless, cerebrospinal fluid evaluation was inconsistently performed, and the retrospective design limited the strength of the conclusions [12].

More recently, Conte et al. described a patient living with HIV who presented with early symptomatic neurosyphilis confirmed by cerebrospinal fluid VDRL positivity. Because the patient declined hospitalization and intravenous therapy, treatment consisted of a single intramuscular dose of benzathine penicillin followed by oral doxycycline (200 mg twice daily for 28 days). Complete clinical recovery was observed, accompanied by progressive serological improvement and cerebrospinal fluid normalization after six months of follow-up. Importantly, benzathine penicillin had been administered before the diagnosis of neurosyphilis was established as treatment for secondary syphilis and therefore was not intentionally incorporated into the neurosyphilis regimen [13].

Collectively, these reports suggest that doxycycline may represent a feasible therapeutic alternative in carefully selected patients for whom standard intravenous penicillin cannot be administered. However, the currently available literature is characterized by marked heterogeneity regarding patient characteristics, HIV status, neurological manifestations, cerebrospinal fluid abnormalities, treatment indications, follow-up duration, and outcome assessment [11–13]. Furthermore, most published patients had early neurosyphilis, and objective neuroimaging findings were inconsistently reported, limiting comparisons across studies [11–13].

The present case expands this limited evidence by describing an elderly HIV-negative patient presenting with progressive vestibulocerebellar dysfunction, pathological nystagmus, gait ataxia, positive Romberg sign, reactive treponemal and non-treponemal serology, and a focal extra-axial neuroimaging abnormality that completely resolved following treatment. Unlike previously reported cases, the patient underwent a deliberately planned outpatient regimen consisting of weekly benzathine penicillin combined with doxycycline for 28 days after refusing hospitalization. The favorable clinical, radiological, and serological evolution observed during long-term follow-up provides additional evidence supporting the potential role of individualized doxycycline-containing regimens when standard intravenous therapy is not feasible, while reinforcing that current guideline-recommended penicillin G therapy remains the standard of care.

DISCUSSION

Neurosyphilis remains one of the most challenging manifestations of *Treponema pallidum* infection because of its protean clinical presentation and the absence of a single diagnostic test with perfect sensitivity and specificity [2,5–8]. Neurological involvement may occur at any stage of syphilis and frequently mimics cerebrovascular, inflammatory, infectious, neoplastic, and degenerative disorders, often delaying diagnosis [1,5,6]. Cerebrospinal fluid (CSF) examination is an important component of the conventional diagnostic assessment of suspected neurosyphilis and was specifically recommended in the present case; however, lumbar puncture could not be performed because the patient declined the procedure despite counseling regarding its diagnostic importance. Accordingly, CSF-VDRL, CSF cellularity, and protein measurements were unavailable. Nevertheless, the diagnosis was supported by a compelling convergence of independent clinical and longitudinal findings: the relatively abrupt development of a previously absent progressive neurological syndrome characterized by dizziness, pathological nystagmus, gait ataxia, disequilibrium, and a positive Romberg sign; strongly reactive serum VDRL (1:64) with positive FTA-ABS; a concurrent focal intracranial imaging abnormality in the absence of preceding trauma; negative investigations for alternative infectious etiologies; and, importantly, a coherent multidomain response following antisyphilitic treatment. Neurological manifestations completely resolved, the extra-axial neuroimaging abnormality disappeared on follow-up imaging, and serum VDRL titers progressively declined from 1:64 to 1:32 and 1:16 before becoming non-reactive at approximately 9 months and remaining non-reactive at 12 months. Although therapeutic response cannot substitute for CSF confirmation and should not be regarded as independently diagnostic, the temporal concordance among clinical onset, syphilis seroreactivity, neurological and radiological abnormalities, treatment, clinical recovery, radiological

resolution, and sustained serological response provides substantial cumulative support for neurosyphilis as the unifying diagnosis in this patient [5,7,8].

An additional distinguishing feature of this case was the presence of a focal extra-axial lesion initially interpreted as a small chronic subdural collection. Neuroimaging abnormalities in neurosyphilis are highly heterogeneous and may include cerebral infarction secondary to meningovascular disease, meningeal enhancement, gummatous lesions, cerebral atrophy, hydrocephalus, and nonspecific white matter abnormalities [5,8]. In contrast, extra-axial collections are distinctly uncommon and are only rarely discussed in the literature. Although the original imaging was no longer available for retrospective review, the spontaneous disappearance of the lesion after antisyphilitic therapy, together with the absence of preceding trauma, suggests that the imaging abnormality was more likely related to the underlying inflammatory process than to an incidental chronic subdural hematoma. This observation further expands the spectrum of radiological manifestations potentially associated with neurosyphilis.

The therapeutic aspect represents the principal contribution of this report. Current international guidelines uniformly recommend intravenous aqueous penicillin G as first-line therapy for neurosyphilis because of its well-established penetration into the central nervous system and decades of accumulated clinical experience [2–4]. Ceftriaxone constitutes the principal recommended alternative when penicillin cannot be administered, and retrospective comparative data suggest clinical outcomes comparable to those achieved with intravenous benzylpenicillin in selected patients [14]. In contrast, doxycycline has received considerably less attention despite favorable pharmacokinetic characteristics, including excellent oral bioavailability, prolonged serum half-life, and the ability to achieve measurable concentrations within the cerebrospinal fluid [9]. Consequently, its use has largely remained restricted to selected clinical circumstances, including penicillin allergy, logistical barriers to prolonged parenteral treatment, or patient refusal of hospitalization.

Our literature review confirms that clinical evidence supporting doxycycline-containing regimens remains remarkably limited. Published experience currently consists primarily of isolated case reports and a single retrospective observational cohort, with no randomized controlled trials available [11–13]. Kang-Birken et al. first described successful treatment of two HIV-positive patients with asymptomatic neurosyphilis using high-dose doxycycline, demonstrating improvement in both cerebrospinal fluid inflammatory parameters and serological markers [11]. Subsequently, Girometti et al. reported favorable clinical and serological outcomes among patients with early neurosyphilis treated with doxycycline, with results comparable to those observed following penicillin-based therapy in a retrospective cohort [12]. More recently, Conte et al. described successful outpatient management of early neurosyphilis in a patient living with HIV who received doxycycline after refusing hospitalization [13]. Collectively, these reports suggest that doxycycline may represent a reasonable alternative in carefully selected circumstances; however, the quality of evidence remains low because of the predominance of observational data, heterogeneous patient populations, and limited long-term follow-up.

The present case differs from previously published reports in several clinically relevant aspects. Our patient was HIV-negative, presented with objective vestibulocerebellar neurological deficits, exhibited an unusual neuroimaging abnormality, and demonstrated complete clinical, radiological, and serological recovery following an intentionally designed outpatient regimen combining benzathine penicillin with doxycycline. Unlike the recently published Brazilian case, in which benzathine penicillin had been administered before recognition of neurosyphilis as treatment for secondary syphilis, combination therapy in our patient represented a deliberate therapeutic strategy after refusal of hospitalization. Although benzathine penicillin alone is not considered adequate treatment for neurosyphilis because it does not achieve therapeutic concentrations within the cerebrospinal fluid, its concomitant administration may have contributed to eradication of systemic infection while doxycycline provided central nervous system antimicrobial activity. Whether this therapeutic combination offers any synergistic benefit cannot be determined from a single observation and requires formal investigation. In addition, systematic reviews of syphilis therapy indicate that evidence supporting doxycycline is largely derived from observational studies, with substantially fewer data than those available for penicillin-based regimens [15,16].

An equally important aspect concerns the diagnostic role of therapeutic response. Although clinical improvement following antimicrobial therapy cannot independently establish the diagnosis of neurosyphilis, the simultaneous resolution of neurological manifestations, disappearance of the intracranial lesion, and progressive decline of serum VDRL titers to complete seroreversion during long-term follow-up substantially reinforce the causal relationship between *Treponema pallidum* infection and the patient's neurological syndrome. The persistence of FTA-ABS positivity throughout follow-up was expected and reflects the well-recognized lifelong persistence of treponemal antibodies despite successful treatment [17].

This report has important limitations. Most importantly, CSF examination could not be performed because the patient declined lumbar puncture despite its recommendation and discussion of its diagnostic value. Consequently, CSF-VDRL reactivity, pleocytosis, and elevated CSF protein—findings conventionally used to support the diagnosis of neurosyphilis—could neither be demonstrated at baseline nor followed after treatment [2,7,8]. This precludes laboratory confirmation of central nervous system infection and should be explicitly acknowledged when interpreting the case. However, the absence of CSF data should be considered within the totality of the longitudinal evidence rather than in isolation: the patient developed a new objective neurological syndrome, had strongly reactive non-treponemal and treponemal serology, demonstrated a contemporaneous intracranial imaging abnormality

without a history of trauma, had no alternative infectious explanation identified, experienced complete neurological recovery following antisyphilitic therapy, showed complete resolution of the imaging abnormality, and demonstrated a progressive VDRL decline culminating in sustained seroreversion. These concordant clinical, radiological, therapeutic, and serological findings substantially strengthen the diagnostic inference, although they do not replace CSF confirmation. Second, the original neuroimaging studies were no longer available for independent reassessment, although the contemporaneous radiological description documented an extra-axial lesion that subsequently resolved after treatment. Third, because this is a single retrospective case reconstructed from contemporaneous medical documentation and the treating physician's clinical records, the findings cannot be generalized beyond the individual patient. Finally, no conclusions regarding comparative efficacy between doxycycline-containing regimens and standard intravenous penicillin therapy can be drawn.

Despite these limitations, this case contributes meaningful evidence to a remarkably sparse literature. It illustrates that, in carefully selected patients who decline hospitalization or cannot receive standard intravenous therapy, an individualized doxycycline-containing regimen may be associated with favorable clinical, radiological, and serological outcomes. Importantly, these observations should not be interpreted as supporting replacement of guideline-recommended intravenous penicillin G but rather as expanding the available clinical experience for exceptional situations in which standard treatment cannot be implemented. Continued improvements in laboratory diagnostic methods and future prospective multicenter registries will be essential to refine diagnostic accuracy and better define the role of doxycycline, alone or in combination with other antimicrobial agents, in the management of neurosyphilis [19].

CONCLUSION

This case-based review highlights the limited evidence currently supporting doxycycline-containing regimens for the treatment of neurosyphilis. In the present patient, an individualized outpatient strategy combining benzathine penicillin and doxycycline was associated with complete clinical recovery, radiological resolution, and sustained serological response after refusal of hospitalization and intravenous therapy. Although these findings add to the growing body of observational evidence suggesting that doxycycline may represent a feasible therapeutic alternative in carefully selected circumstances, they should not be interpreted as replacing guideline-recommended intravenous aqueous penicillin G. Rather, this report expands the available clinical experience for exceptional situations in which standard therapy cannot be administered. Further prospective studies and multicenter registries are needed to better define the efficacy, safety, and optimal role of doxycycline-containing regimens in the management of neurosyphilis.

DECLARATIONS

Ethics approval

This case-based review was prepared in accordance with the ethical principles of the Declaration of Helsinki. The patient is deceased, and all potentially identifying information has been removed from the manuscript.

Consent for publication

The patient is deceased and therefore could not provide written informed consent for publication. No directly identifiable personal information, photographs, or original neuroimaging containing patient identifiers are included in this report.

Availability of data and materials

The clinical data supporting this case are contained within the article. Additional patient-level data are not publicly available because of confidentiality and privacy considerations.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

The authors contributed to the conception and design of the study, acquisition and interpretation of clinical data, literature review, drafting of the manuscript, and critical revision for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

None.

Use of artificial intelligence

Generative artificial intelligence was used solely to assist with language editing and improvement of manuscript clarity. All scientific content, clinical interpretation, literature assessment, and conclusions were critically reviewed and verified by the authors, who take full responsibility for the final content of the manuscript.

REFERENCES

1. Ghanem KG, Ram S, Rice PA. The Modern Epidemic of Syphilis. N Engl J Med. 2020 Feb 27;382(9):845-854. doi: 10.1056/NEJMra1901593. PMID: 32101666.

2. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. doi: 10.15585/mmwr.rr7004a1. Erratum in: MMWR Morb Mortal Wkly Rep. 2023 Jan 27;72(4):107-108. doi: 10.15585/mmwr.mm7204a5. PMID: 34292926; PMCID: PMC8344968.
3. Janier M, Unemo M, Dupin N, Tiplica GS, Potočnik M, Patel R. 2020 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2021 Mar;35(3):574-588. doi: 10.1111/jdv.16946. Epub 2020 Oct 22. PMID: 33094521.
4. Kingston M, French P, Higgins S, McQuillan O, Sukthankar A, Stott C et al. UK national guidelines on the management of syphilis 2015. Int J STD AIDS. 2016 May;27(6):421-46. doi: 10.1177/0956462415624059. Epub 2015 Dec 31. PMID: 26721608.
5. Ropper AH. Neurosyphilis. N Engl J Med. 2019 Oct 3;381(14):1358-1363. doi: 10.1056/NEJMra1906228. Erratum in: N Engl J Med. 2019 Oct 31;381(18):1789. doi: 10.1056/NEJMx190030. Erratum in: N Engl J Med. 2023 Nov 9;389(19):1828. doi: 10.1056/NEJMx230008. PMID: 31577877.
6. Tuddenham S, Ghanem KG. Neurosyphilis: Knowledge Gaps and Controversies. Sex Transm Dis. 2018 Mar;45(3):147-151. doi: 10.1097/OLQ.0000000000000723. PMID: 29420441; PMCID: PMC5808573.
7. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. Sex Transm Dis. 2012 Apr;39(4):291-7. doi: 10.1097/OLQ.0b013e31824c0e62. PMID: 22421696.
8. Boog GHP, Lopes JVZ, Mahler JV, Solti M, Kawahara LT, Teng AK, Munhoz JVT, Levin AS. Diagnostic tools for neurosyphilis: a systematic review. BMC Infect Dis. 2021 Jun 14;21(1):568. doi: 10.1186/s12879-021-06264-8. PMID: 34126948; PMCID: PMC8201870.
9. Yim CW, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. Antimicrob Agents Chemother. 1985 Aug;28(2):347-8. doi: 10.1128/AAC.28.2.347. PMID: 3834836; PMCID: PMC180244.
10. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, Tugwell P, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218-235. doi:10.1016/j.jclinepi.2017.04.026.
11. Kang-Birken SL, Castel U, Prichard JG. Oral doxycycline for treatment of neurosyphilis in two patients infected with human immunodeficiency virus. Pharmacotherapy. 2010 Apr;30(4):119e-122e. doi: 10.1592/phco.30.4.418. PMID: 20334461.
12. Girometti N, Junejo MH, Nugent D, McOwan A, Whitlock G; 56 Dean Street Collaborative Group. Clinical and serological outcomes in patients treated with oral doxycycline for early neurosyphilis. J Antimicrob Chemother. 2021 Jun 18;76(7):1916-1919. doi: 10.1093/jac/dkab100. PMID: 33783506.
13. Conte BP, Silveira RL, Pedro FL, Corazza JM, Santos FCV. Oral doxycycline as an alternative treatment for early neurosyphilis in a patient living with HIV. Infectologia em Evidência. 2024;3:e20240947. doi:10.5935/2764-734X.e20240947.
14. Bettuzzi T, Jourdes A, Robineau O, Alcaraz I, Manda V, Molina JM, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. Lancet Infect Dis. 2021 Oct;21(10):1441-1447. doi: 10.1016/S1473-3099(20)30857-4. Epub 2021 May 26. Erratum in: Lancet Infect Dis. 2021 Oct;21(10):e302. doi: 10.1016/S1473-3099(21)00477-1. PMID: 34051142.
15. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014 Nov 12;312(18):1905-17. doi: 10.1001/jama.2014.13259. PMID: 25387188; PMCID: PMC6690208.
16. Dai T, Qu R, Liu J, Zhou P, Wang Q. Efficacy of Doxycycline in the Treatment of Syphilis. Antimicrob Agents Chemother. 2016 Dec 27;61(1):e01092-16. doi: 10.1128/AAC.01092-16. PMID: 27795370; PMCID: PMC5192147.
17. Li J, Zheng HY. Early syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. J Infect Dev Ctries. 2014 Feb 13;8(2):228-32. doi: 10.3855/jidc.3013. PMID: 24518634.
18. Lewis DA, Lukehart SA. Antimicrobial resistance in Neisseria gonorrhoeae and Treponema pallidum: evolution, therapeutic challenges and the need to strengthen global surveillance. Sex Transm Infect. 2011 Dec;87 Suppl 2(Suppl 2):ii39-43. doi: 10.1136/sti.2010.047712. PMID: 22110154; PMCID: PMC3610386.
19. Luo Y, Xie Y, Xiao Y. Laboratory Diagnostic Tools for Syphilis: Current Status and Future Prospects. Front Cell Infect Microbiol. 2021 Feb 8;10:574806. doi: 10.3389/fcimb.2020.574806. PMID: 33628742; PMCID: PMC7897658.

Table 1. Published cases and series of neurosyphilis treated with doxycycline-containing regimens, including the present case.

Author, year	Country	Design	N	Age/sex	HIV status	Type of neurosyphilis	Main symptoms	Neurological exam	Serum VDRL/RPR	CSF findings	Neuroimaging	Standard IV penicillin used?	Doxycycline regimen	Benzathine penicillin	Reason for non-standard regimen	Clinical outcome	Serologic outcome	CSF outcome	Radiologic outcome	Follow-up
Kang-Birken et al., 2010 [11]	USA	Case report	2	45/M; 37/M	HIV+	Asymptomatic neurosyphilis	None	Not reported	1:128; 1:64	Case 1: CSF VDRL 1:16, WBC 96/mm³, protein 89 mg/dL. Case 2: CSF VDRL negative, WBC 29/mm³, protein 46 mg/dL	Not reported	No	Doxycycline 200 mg BID × 28 days	No	Alternative to IV/IM penicillin	Remained clinically well	VDRL declined	CSF improved/normalized	Not reported	2–3 months
Girometti et al., 2021 [12]	UK	Retrospective cohort	87 total; 16 doxycycline	Median 35 years	53% HIV+ overall	Early neurosyphilis	Headache, visual symptoms, hearing impairment, tinnitus, vertigo/dizziness, unsteady gait	Variable; focal symptoms included	Median RPR 1:64 in doxycycline group	LP performed in 52/87; 7/16 doxycycline patients	Not routinely reported	No, in doxycycline group	Doxycycline 200 mg BID × 28 days	No	Declined IM therapy, inability to attend injections, penicillin allergy, physician decision	100% clinical response in doxycycline group	100% serologic response	Limited CSF follow-up	Not reported	Up to 12 months
Conte et al., 2024 [13]	Brazil	Case report	1	39/M	HIV+	Early neurosyphilis	Rash, nausea/vomiting, dizziness, amaurosis, paresthesia, syncope, dorsalgia	No major abnormalities described	Serum VDRL 1:16	CSF VDRL 1:16, 5 cells, protein 40 mg/dL, glucose 64 mg/dL	Not reported	No	Doxycycline 200 mg BID × 28 days	Single dose 2.4 MU IM before neurosyphilis diagnosis	Refused hospitalization and ceftriaxone	Complete symptom resolution	Serum VDRL decreased	CSF VDRL negative at 6 months	Not reported	6 months
Present case	Brazil	Case report / case-	1	81/M	HIV negative	Symptomatic neurosyphilis with	Progressive dizziness, imbalanc	Pathological nystagmus,	VDRL 1:64; FTA-ABS	Lumbar puncture	CT showed extra-axial	No	Doxycycline 100 mg	2.4 MU IM weekly	Refused hospitalization for IV	Complete neurological	Progressive VDRL declin	Not available	Complete resolution	Long-term

Author, year	Country	Design	N	Age/sex	HIV status	Type of neurosyphilis	Main symptoms	Neurological exam	Serum VDRL/RPR	CSF findings	Neuroimaging	Standard IV penicillin used?	Doxycycline regimen	Benzathine penicillin	Reason for non-standard regimen	Clinical outcome	Serologic outcome	CSF outcome	Radiologic outcome	Follow-up
		based review				cerebellar/vestibular syndrome	e, gait difficulty, fall risk	positive Romberg, gait ataxia; no motor/sensory deficit	positive	declined	lesion suggestive of subdural collection; resolved after treatment		BID × 28 days	× 3 weeks	penicillin and lumbar puncture	recovery	e to non-reactive by 9–12 months		on control imaging	clinical follow-up