SAGE Open Medical Case Reports
Volume 12: 1–7

DOI: 10.1177/2050313X241256825
journals.sagepub.com/home/sco
Sage

Neurosyphilis with sequential respiratory complications: A case report highlighting diagnostic and treatment challenges

Hanifa Majid[1], Sajjad Ali[2], Fatima A Raza[3], Sidra Jabeen[4], Habiba Majid[3], Areeba Sheikh[1] and Muzamil Ahmed[1]

Abstract

In this case report, we describe the presentation and clinical course of a 25-year-old male with a complex medical history and a fatal outcome due to neurosyphilis. The diagnosis of neurosyphilis-related complications. Neurosyphilis, a variant of tertiary syphilis, is a rare condition but can present with a wide range of neurological symptoms. This makes its diagnosis challenging. The study aims to report and discuss neurosyphilis in a young male, resulting in respiratory complications, and explore the clinical presentation, diagnostic and process, treatment challenges it poses to a tertiary care setup of a third-world country regimen, and the profound significance of this particular case.

Keywords

Neurosyphilis, respiratory, complications, *Treponema pallidum*

Date received: 6 January 2024; accepted: 6 May 2024

Introduction

Syphilis is caused by a bacteria, *Treponema pallidum (T. pallidum)*, which passes through various stages of medical presentation.[1] Nearly all cases of syphilis are spread by vaginal, ano-genital, and oro-genital contact. The overall incidence of syphilis declined after the discovery/invention of penicillin and the implementation of public health care measures. However, the number of cases has started to rise again along with HIV infection, with which syphilis shares a synergistic relationship.[2,3]

Syphilis is referred to as "the great imitator" due to its extensive clinical manifestations, which may resemble those of other illnesses.[3] It can be classified into primary, secondary, and tertiary syphilis, with neurosyphilis (NS) being a variant of tertiary syphilis. Nervous system (NS) can be divided into early or late NS, and it presents with numerous distinctive symptoms, such as seizures, cranial nerve defects, emotional instability, difficulties with memory, and cognition impairment.[4] The prevalence of acute symptomatic seizures secondary to NS is highly variable and could range from 14% to 60%.[5,6] Status epilepticus is regarded as one of the infrequent and lethal manifestations of NS, and only a few case reports have been published until now. After the discovery of penicillin, cases of tertiary syphilis have been reduced, but some cases of central nervous system (CNS) or spinal involvement are still reported occasionally.[7–9]

In this case report, we describe the presentation and clinical course of a 25-year-old male with a complex medical history and a fatal outcome due to NS-related complications. The study aims to explore the clinical presentation, diagnostic process, treatment regimen, and the profound significance of this particular case.

[1]Dow University of Health Sciences, Karachi, Pakistan
[2]Ziauddin Medical College, Ziauddin University, Karachi, Pakistan
[3]Karachi Medical and Dental College, Karachi, Pakistan
[4]Liaqat National Hospital, Karachi, Pakistan

Corresponding Author:
Sajjad Ali, Ziauddin Medical College, Ziauddin University, 4/B Shahrah-e-Ghalib Rd, Block 6 Clifton, Karachi 75000, Pakistan.
Email: sajjad110@live.com

Case presentation

A 25-year-old male with no known comorbidities was brought unconscious to the emergency room on April 6, 2023 at our hospital with complaints of headache for the last 3 years, fever, and altered level of consciousness (ALOC) over the previous 10 days. The headache that started 3 years back was moderate to severe and occurred throughout the day, more localized toward the frontal region and relieved by analgesics. Such episodes occurred every week. The fever that started 10 days back was sudden, high-grade, continuous without rigors or chills, and relieved by medication temporarily. It was associated with headaches and episodes of vomiting that were non-projectile and contained food he ingested. During his journey to Hyderabad, he developed ALOC, which started with irritability, and later, he became unresponsive, after which the patient was brought to our hospital. During his course of initial stay, he developed generalized tonic-clonic seizure that was associated with frothing. The patient has no history of trauma, dysphagia, blurring of vision, diplopia, or urinary/fecal incontinence. He has had a sexual history with males and donkeys. His medical and family history were unremarkable. Although the source of the patient's exposure *to T. pallidum* remains unclear, it is suspected that it may have been related to his trip to Hyderabad, or the complex sexual history noted upon history taking.

The patient's initial vital signs upon presentation were as follows: fever of 102 F, a heart rate of 110 beats per minute, a blood pressure of 105/60 mmHg, an oxygen saturation level of 92%, and a respiratory rate of 22 breaths per minute. The patient was kept on the Synchronized Intermittent Mandatory ventilator (SIMV) and had a Glasgow Coma Scale (GCS) of 3/10. On cranial nerve examination, his pupils were reactive, doll eyes were positive, and brainstem reflexes were diminished. On motor examination, his bulk and tone are normal, and his power is moving all four limbs, 1+ reflexes, and mute plantar reflex.

Cerebrospinal fluid drainage (CSF DR) revealed the following results: glucose was 66 mg/dl (RBS = 250 mg/dl), protein was 85 mg/dl, white blood cells 0.022×10^9/L neutrophils were 5%, lymphocytes were 90% and monocytes were 5%. His anti-nuclear antibodies test came positive, and his syphilis antibody test (ECLIA) and Treponema Pallidum Hemagglutination Assay both were reactive while he was negative for HIV, hepatitis B and C, and tuberculosis. Although there is an absence of standardized testing for NS, the diagnosis was made based on the current Center for Disease Control recommendations, where NS is confirmed for patients diagnosed with syphilis, report neurological symptoms, and demonstrate abnormal CSF findings.[10]

The patient was initially treated with Intravenous (IV) Meropenem 1g thrice a day (TDS), IV Vancomycin 1g twice a day (BD), IV Acyclovir 750 mg TDS and IV Dexamethasone 8 mg BD as a viral infection had been suspected, necessitating prompt management. However, after being diagnosed as a case of NS he was started on IV Benzyl Penicillin G 4MU every 4 hourly.

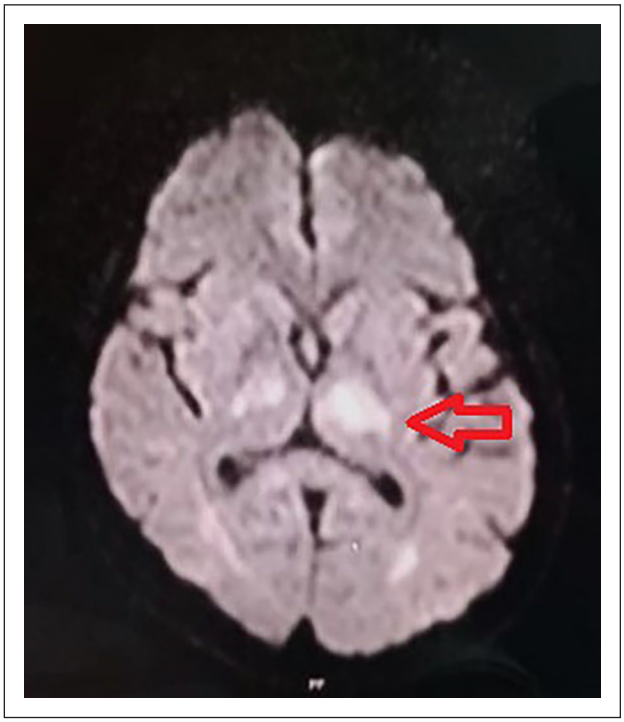

Figure 1. Post-contrast magnetic resonance imaging showing abnormal signal intensity areas involving bilateral basal ganglia, thalami, and periventricular deep white matter (red arrow).

A magnetic resonance imaging (MRI) scan of the brain was done on the third day of admission. It showed abnormal signal intensity areas involving bilateral basal ganglia, thalami, and periventricular deep white matter (Figure 1). A non-enhancing, fluid signal intensity area in the white matter of the right parietal lobe shows peripheral high signal and restriction (Figure 2). Moreover, magnetic resonance angiography (MRA) of the brain was done, which showed leptomeningeal enhancement in the right parieto-occipital region, representing leptomeningitis.

Between initial hospitalization and the 6th week of hospitalization, there was no improvement in the scoring of GCS and patient was administered IV Benzyl Penicillin G 4MU every 4 h. On the 6th week of hospitalization, the patient developed spontaneous left-sided pneumothorax. ABGs showed pO2 (227 mmHg), pCO2 (118 mmHg), and bicarbonate (39.3 mmol/L). Chest X-ray showed worsening left-sided pneumothorax and right-sided consolidation (Figure 3). His GCS remained stable at 3/10. The pupils were bilaterally equally reactive to light, with the right eye laterally deviated forward. There was decreased bilateral bulk and tone on motor examination with no power and reflexes. All signs were consistent with brain death. The family was counseled regarding the patient's prognosis, and he was disconnected from the ventilator.

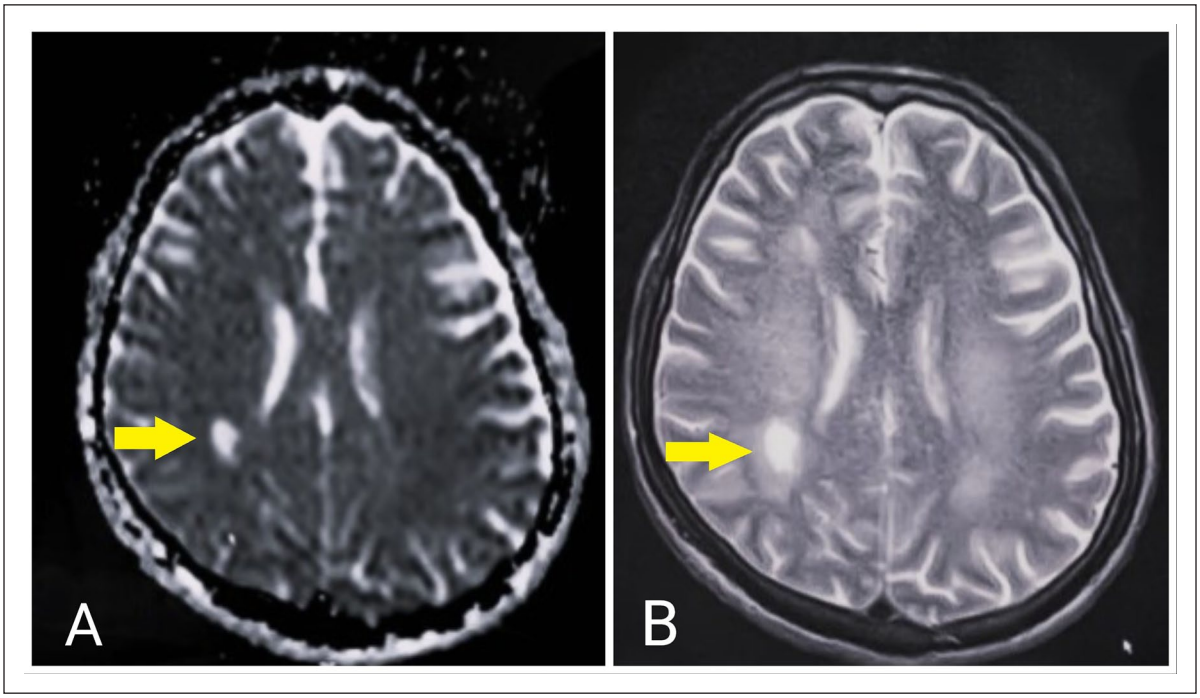

Figure 2. An MRI of the brain; (A) without contrast and (B) with contrast. A non-enhancing, fluid signal intensity area in the white matter of the Right Parietal lobe shows peripheral high signal and restriction (yellow arrow).

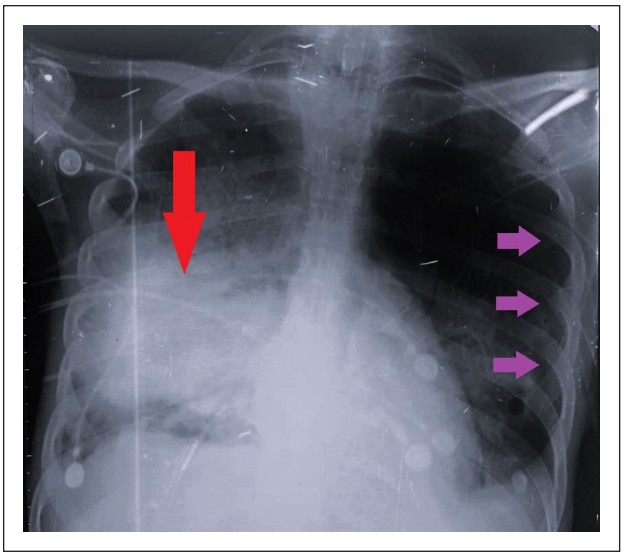

Figure 3. An anterior/posterior view of the chest X-ray showing right-sided consolidation (red arrow) and left-sided pneumothorax (purple arrows).

Discussion

The current study summarized the neurological manifestations that may occur during the course of the disease and presented a case diagnosed with NS, which may aid in the condition's more rapid diagnosis as clinical diagnosis of NS is still far from ideal. Because of its wide range of possible appearances, NS is one of the most challenging conditions to identify in patients without a known history of syphilis infection.

In our case study, our patient's initial complaints of severe headaches, fever, and ALOC are common neurological symptoms seen in NS. The recurring, severe headaches localized in the frontal region were likely indicative of NS involvement in the CNS, but that has not been seen usually in syphilis cases. The development of ALOC probably indicates significant CNS involvement. ALOC evolving from irritability to complete unresponsiveness is a crucial clinical finding not commonly seen in such patients. Such findings made the diagnosis challenging.

In a study done by Drago et al.[11] on 286 syphilitic patients, with 141 cases (49%), general paresis was the most prevalent manifestation. Cognitive impairment, behavioral abnormalities, dementia, depression, mania, and psychosis with auditory or visual hallucinations were other common signs. Similar results were revealed by an older study done by Conde-Sendín et al.[12] A study by Lee et al.[13] also found a similar presentation in 24 syphilitic patients. All of these symptoms, however, were not present in our case.

The imaging studies, including post-contrast MRI and MRA, provided critical information about the extent of CNS involvement. Abnormal signal intensities in the basal ganglia, thalami, and periventricular deep white matter observed in the MRI are consistent with NS-related CNS pathology. Leptomeningeal enhancement seen in the MRA represents leptomeningitis, further supporting the diagnosis.[13]

After the initial infection, the CNS may get involved months, years, or even decades later. Less than a day after the first syphilitic infection, *T. pallidum* enters the CNS by hematogenic and lymphatic spread, causing perivascular and leptomeningeal inflammation, according to data from animal models.[14,15] *T. pallidum* is frequently found in the CSF of people with latent and early-stage syphilis with various techniques such as polymerase chain reaction.[16] A study from Japan showed these bacteria in the CSF of 28.6% of patients with primary and secondary syphilis, which is suggestive of an early CNS invasion by *T. pallidum*.[17]

A gold standard for NS diagnosis does not yet exist. Different recommendations indicate the use of treponemal and nontreponemal diagnostics and the appropriateness of lumbar punctures in syphilitic patients. As a result, the diagnosis is made using a combination of neuroimaging, CSF abnormalities, clinical symptoms, and diagnostic testing, and a similar approach was used for this case. For this reason, NS is currently considered a significant clinical challenge, and brain MRI may be recommended as a helpful diagnostic technique in the differential diagnosis of NS.[14,18] Scholarly publications suggest that some findings in the NS, such as atrophy, white matter lesions, cerebral infarction, medium contrast enhancement, and edema, may be more specific.[14,19] These were consistent findings in our case as well.

Multiple studies have shown a prevalent occurrence of the meningovascular type of NS, leading to direct imaging evidence of cerebral vasculitis and cerebral infarctions, particularly in the brainstem or basal ganglia.[18–20] The middle cerebral artery and basilar artery branches are the most commonly observed abnormalities in NS.[18,21] A few researchers have found hyperintensities on MRI of the mesial temporal regions, which mimic viral encephalitis.[22,23] NS can be distinguished from encephalitis by the coexistence of atrophy and temporal horn enlargement instead of edema. It has been established that one characteristic of the general paresis of the insane is selective atrophy of the mesial temporal structures.[23]

Furthermore, we reviewed and compiled all of the NS cases, looking at their age, gender, chief complaints, and site of myelitis, as well as their treatment plans and outcomes. In addition, we did a thorough literature search on the PubMed database for all studies with full text available in English and original data on NS patients published in the last 5 years, from January 2017 to October 2023. We searched using the following keywords: NS, *Treponema pallidum*, myelitis, and prognosis. As a result, we found a total of 9 published articles with 12 NS cases (Table 1).

The unfortunate outcome of the presented case illustrates the potential grave respiratory consequences of NS. Despite initial supportive care and targeted antibiotic therapy, the patient encountered severe pulmonary complications, specifically the development of spontaneous left-sided pneumothorax, escalating to respiratory failure and right-sided consolidation. The subsequent decline in gas exchange parameters, indicated by ABG findings showcasing severe hypoxemia and hypercapnia, emphasized the critical impact on pulmonary function. These grave complications, accentuated by the evolving chest X-ray abnormalities, ultimately contributed to the patient's demise, underscoring the criticality of comprehensive monitoring and prompt intervention in cases of NS with respiratory involvement. However, since respiratory complications could have possibly been ventilator-related or due to pneumonia infection, which could result from a nosocomial infection after a 6-week stay at the hospital, a definite association between NS and respiratory complications could not be established by our report. Therefore, there is a need for further research to compare the presence of respiratory complications in NS patients who required ventilators and those who did not to enhance their outcomes and reduce mortality rates.

Conclusion

This case emphasizes the need for healthcare providers to maintain a high index of suspicion for syphilis, particularly when evaluating patients with unexplained neurological symptoms. Timely diagnosis and appropriate treatment are essential to prevent the progression of NS and its potentially devastating consequences. Our case also highlights a potential association between respiratory complications and NS infection, which sheds the light on the need for future research to investigate such an association for improving patient outcomes.

Table 1. Review of the literature on NS-related cases in the last 5 years.

Study	Gender	Age (years)	Chief complaints	Site of myelitis/condition	Treatment	Outcomes
Krishnan[24]	Male	39	Sudden onset of speech difficulty, mild dull constant headache for a week, transient right facial asymmetry	Left middle cerebral	Initiated in intravenous (IV) benzylpenicillin as per protocol for neurosyphilis (NS)	Showed good recovery after treatment with IV benzylpenicillin
Fernandes[25]	Male	44	Initially, insomnia and fatigue, followed by intense, diffuse, recurrent abdominal pain, anorexia, unquantified weight loss, suicidal ideation	No specific mention of myelitis	Benzylpenicillin administered for 14 days	Progressive clinical improvement throughout treatment, remission of anxiety and delusions, regularization of sleep and appetite patterns, decreasing rapid regain (RPR) titers
Liao[26]	Female	62	Paroxysmal falls, impaired consciousness, limb twitch, gibberish speech	None mentioned	Penicillin G sodium administered intravenously for 14 days (multiple courses)	Significant improvement in clinical symptoms, remission of seizures, normal cognitive function, decrease in LGI1 antibody titer, disappearance of abdominal MRI signals in the right medial temporal lobe
Chandrasekharan[27]	Male	50	Gradually progressive hearing diminution in the left ear, occasional tinnitus, followed by difficulty closing the left eye and drooling of food and saliva through the left side of the mouth	The report does not explicitly mention myelitis or its specific site	IV penicillin G, 4 million units every 4 h for 6 weeks	Mild improvement in hearing and other cranial nerve symptoms. Significant reduction in the size of the extradural soft tissue at the pre-medullary cistern and cerebellopontine angle observed during follow-up. Some improvement in cranial nerve palsies, but the hearing loss had not improved further
Green[28]	Male	33	Progressive headache and diplopia	Isolated left cranial nerve VI palsy	IV Penicillin G for 14 days	Resolution of headache, partial improvement in left cranial nerve VI palsy.
	Male	56	Acute confusion	Cystic infarcts (bilateral basal ganglia	IV Benzylpenicillin for 14 days	Significant improvement, improvement in cognitive testing, Montreal Cognitive Assessment (MOCA) score returned to baseline, ongoing effects on long-term recall
Zhang[29]	Female	59	Presented with bradyglossia and weakness of the right lower limb.	She was diagnosed with NS, presenting as a progressive stroke	Administered aspirin, clopidogrel, atorvastatin, butylphthalide, edaravone, roxithromycin, and doxycycline. Hexadecadrol was also initiated	The patient's symptoms deteriorated twice after treatment initiation, experiencing severe diarrhea and a decline in muscle strength on the right side. Clinical symptoms did not improve significantly after 14 days of antibiotic treatment, and she was discharged for further treatment at a venereal disease hospital
Seay[30]	Male	56	Periumbilical abdominal pain, nausea, and constipation	NS manifested as Syndrome of Inappropriate Antidiuretic Hormone Secretion	Penicillin desensitization followed by a 14-day course of penicillin G	Recovery of sodium to normal range on discharge; resolved constipation and nausea; normal sodium levels maintained after discharge; successful completion of penicillin treatment; follow-up showing improvement with decreasing RPR titers over time
Roy[31]	Male	25	Sudden painless vision loss in the left eye for 20 days	Optic neuritis in the left eye due to NS	Injectable ceftriaxone 2 g intravenously for 14 days along with injectable corticosteroids initially, followed by oral corticosteroids as per the schedule of optic neuritis	Vision gradually improved within 1 month, reaching 6/9 in the left eye; recurrence of blurring of vision after a month, followed by extensive serum biochemical and serological tests and cerebrospinal fluid (CSF) analysis confirming NS; further treatment with injectable ceftriaxone led to improvement in vision; subsequent improvement and decrease in high Treponema pallidum hemagglutination assay and RPR titers in blood and CSF at the 3-month follow-up.
Balaban[32]	Male	28	Jacksonian epileptic episodes in the left arm	Cortical, parietal lesion detected in brain MRI	Penicillin G crystalline followed by Benzathine Penicillin	There was no improvement initially; increased antiepileptic dose led to the complete disappearance of Jacksonian episodes.
	Male	76	Generalized tonic-clonic episodes	Subacute ischemic lesion in the left middle cerebral artery territory	Penicillin G crystalline followed by Benzathine Penicillin	Severe cognitive impairment initially, improved after treatment. Continued intramuscular Benzathine Penicillin advised
	Male	51	Sudden established speech difficulty, left leg motor weakness	Not explicitly mentioned	Penicillin G crystalline followed by Benzathine Penicillin	Mild cognitive impairment initially, progressed over time. Continued treatment with additional medication due to cognitive decline

Acknowledgements

None.

Author contributions

H.M. contributed to Conceptualization, Writing-Original Draft, Visualization; S.A. contributed to Writing-Original Draft, Writing-Review & Editing, Formal Analysis; F.A.R. contributed to Writing-Original Draft, Writing-Review & Editing, Resources, Data Curation; S.J. contributed to Writing-Review & Editing, Resources, Investigation, Methodology; H.M. contributed to Writing-Review & Editing, Software, Funding Acquisition; A.S. contributed to Writing-Review & Editing, Visualization, Formal Analysis; M.A. contributed to Writing-Review & Editing, Funding Acquisition, Investigation, Project Administration.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

ORCID iD

Sajjad Ali https://orcid.org/0000-0002-8024-5942

References

1. Golden MR, Marra CM and Holmes KK. Update on syphilis: resurgence of an old problem. *JAMA* 2003; 290(11): 1510–1514.
2. Gjestland T. The Oslo study of untreated syphilis, an epidemiologic investigation of the natural course of syphilitic infection based upon a restudy of the Boeck-Bruusgaard material. *Acta Derm Venereol* 1955; 35: S-34.
3. Tuddenham S and Ghanem KG. Neurosyphilis: knowledge gaps and controversies. *Sex Transm Dis* 2018; 45(3): 147–151.
4. Landry T, Smyczek P, Cooper R, et al. Retrospective review of tertiary and neurosyphilis cases in Alberta, 1973–2017. *BMJ Open* 2019; 9(6): e025995.
5. Tong ML, Liu LL, Zeng YL, et al. Laboratory findings in neurosyphilis patients with epileptic seizures alone as the initial presenting symptom. *Diagn Microbiol Infect Dis* 2013; 75(4): 377–380.
6. Ances BM, Shellhaus R, Brown MJ, et al. Neurosyphilis and status epilepticus: case report and literature review. *Epilepsy Res* 2004; 59(1): 67–70.
7. Cozzani E, Gasparini G, Ciccarese G, et al. Concurrent benign tertiary syphilis and asymptomatic neurosyphilis in an immunocompetent patient. *J Eur Acad Dermatol Venereol* 2021; 35(2): e151–e152.
8. Bai Y, Niu F, Liu L, et al. Tertiary syphilis in the lumbar spine: a case report. *BMC Infectious Diseases* 2017; 17(1): 1–4.
9. Salem KM, Majeed H, Bommireddy R, et al. Tertiary syphilis in the cervical spine: a case report and review of the literature. *Glob Spine J* 2013; 3(1): 041-6.
10. Ha T, Prasanna Tadi and Dubensky L. Neurosyphilis. *Nih.gov*, https://www.ncbi.nlm.nih.gov/books/NBK540979/ (2019).
11. Drago F, Merlo G, Ciccarese G, et al. Changes in neurosyphilis presentation: a survey on 286 patients. *J Eur Acad Dermatol Venereol* 2016; 30(11): 1886–1900.
12. Conde-Sendín MÁ, Amela-Peris R, Aladro-Benito Y, et al. Current clinical spectrum of neurosyphilis in immunocompetent patients. *Eur Neurol* 2004; 52(1): 29–35.
13. Lee JB, Kim SC, Lee S, et al. Symptomatic neurosyphilis. *Int J Dermatol* 1983; 22(10): 577–580.
14. Corrêa DG, de Souza SR, Freddi TAL, et al. Imaging features of neurosyphilis. *J Neuroradiol* 2023; 50(2): 241–252.
15. LaFond RE and Lukehart SA. Biological basis for syphilis. *Clin Microbiol Rev* 2006; 19(1): 29–49.
16. Castro R, Águas MJ, Batista T, et al. Detection of *Treponema pallidum* sp. pallidum DNA in cerebrospinal fluid (CSF) by two PCR techniques. *J Clin Lab Anal* 2016; 30(5): 628–632.
17. Hagihara M, Yamagishi Y, Kato H, et al. Frequency of 7*Treponema pallidum* invasion into cerebrospinal fluid in primary or secondary early-stage syphilis. *J Infect Chemother* 2018; 24(5): 404–406.
18. Czarnowska-Cubała M. Neurosyphilis and brain magnetic resonance imaging. *Int J Dermatol* 2015; 54(7): 863.
19. Czarnowska-Cubała M, S Wiglusz M, Jerzy Cubała W, et al. MR findings in neurosyphilis–a literature review with a focus on a practical approach to neuroimaging. *Psychiatr Danubina* 2013; 25(suppl 2): 153–157.
20. Kasanuki K, Iseki E, Fujishiro H, et al. P4–113: a case of neurosyphilis with dementia and occipital lobe hypometabolism on 18FFDG-PET. *Alzheimer Dementia* 2013; 9: P745-P.
21. Pichler R, Doppler S, Szalay E, et al. SPECT and FDG-PET in diagnostics of neurolues. *Wiener klinische Wochenschrift* 2008; 120: 20–23.
22. Tiwana H and Ahmed A. Neurosyphilis: mighty imitator forays with benign presentation and unique neuroimaging findings. *Sex Health* 2018; 15(4): 358–360.
23. Nagappa M, Sinha S, Taly A, et al. Neurosyphilis: MRI features and their phenotypic correlation in a cohort of 35 patients from a tertiary care university hospital. *Neuroradiology* 2013; 55: 379–388.
24. Krishnan D, Zaini SS, Latif KA, et al. Neurosyphilis presenting as acute ischemic stroke. *Clin Med (Lond)* 2020; 20(1): 95–97.
25. Fernandes NA, Martins MA, Ferreira LP, et al. An atypical case of neurosyphilis. *Prim Care Companion CNS Disord* 2020; 22(6), 26628.
26. Liao H, Zhang Y and Yue W. Case report: a Case Report of Neurosyphilis Mimicking Limbic Encephalitis. *Front Neurol* 2022; 13: 862175.
27. Chandrasekharan R, Kulkarni C, Pullara SK, et al. Magnetic resonance imaging in otosyphilis: a Rare Manifestation

of Neurosyphilis. *Indian J Radiol Imaging* 2022; 32(2): 278–284.
28. Green J, Savage N, Jenkins C, et al. Lesson of the month 1: neurosyphilis mimicking viral encephalitis and ischaemic stroke. *Clin Med (Lond)* 2019; 19(3): 252–254.
29. Zhang K, Chu F, Wang C, et al. Progressive stroke caused by neurosyphilis with concentric enhancement in the internal cerebral artery on high-resolution magnetic resonance imaging: a case report. *Front Neurol* 2021; 12: 675083.
30. Seay HL, Khallouf L, Lieberman A, et al. An unusual case of neurosyphilis manifesting as syndrome of inappropriate antidiuretic hormone secretion (SIADH). *Am J Case Rep* 2021; 22: e929050.
31. Roy T, Gupta AD and Islam AR. Optic neuritis presented as the only manifestation of neurosyphilis. *Oman J Ophthalmol* 2023; 16(1): 161–164.
32. Codreanu Balaban RA, Axelerad A, Musat D, et al. Three cases of neurosyphilis diagnosed in the 21st century: a case report. *Exp Ther Med* 2023; 25(5): 201.