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Neurosyphilis: A Comprehensive Review of Clinical Manifestations, Diagnosis, and Treatment

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Abstract

Neurosyphilis, a sexually transmitted infection caused by *Treponema pallidum*, occurs when this organism breaches the central nervous system, particularly in individuals with compromised immune systems such as those living with HIV. Neurosyphilis remains a global health concern, and its prevalence has risen significantly, particularly among men who have sex with men (MSM) and among immunocompromised people, highlighting the importance of screening and public health interventions. Although neuroinvasion may happen at an early stage, the clinical signs might not appear until years later. Clinical presentations can differ from asymptomatic cases to serious complications such as meningitis and cognitive deficits. Diagnosis mainly relies on serological and cerebrospinal fluid (CSF) analysis. Penicillin remains the drug of choice, but alternative therapies may be necessary for penicillin allergy. Early detection and treatment significantly improve prognosis; however, late-stage cases may lead to permanent neurological damage. Increasing public awareness, providing education, and advancing research on diagnostic and treatment methods are essential to address the challenges of this re-emerging disease.

Keywords: Neurosyphilis; *Treponema pallidum*; Sexually transmitted infections (STIs); Central nervous system (CNS) involvement; HIV and neurosyphilis

1 Introduction

Syphilis is caused by the spirochete *Treponema pallidum*. The primary and secondary stages affect skin and mucous membranes. If left untreated, the pathogen invades the CNS, resulting in neurosyphilis.[1] Neurosyphilis can develop at any stage following the initial infection and is usually the result of untreated or inadequately treated

syphilis. Although early neuroinvasion by *T. pallidum* is common, clinical symptoms appear only when spirochetes persist in the CNS.[2] Neurosyphilis comprises a spectrum of clinical presentations, ranging from asymptomatic cases to life-threatening conditions, and warrants early recognition and treatment to avoid permanent neurological damage.[3]

2 Epidemiology

Between 1990 and 2019, the number of people infected with syphilis increased by 60% worldwide, leading to approximately 50 million infections in 2019.[4] According to the World Health Organization (WHO), there were roughly 7.1 million new cases of syphilis worldwide in 2020.[5] Syphilis rates have decreased with the advent of penicillin, but both positive and negative trends have been observed in recent decades, especially among men who have sex with men (MSM) and HIV-positive populations.[1] MSM suffer syphilis rates 15 to 20 times greater than other men, and about half of them are HIV co-infected. Approximately one-third of patients with syphilis develop neurosyphilis before antibiotic use.[6] It is now more common in people with HIV, especially in those with low CD4+ counts or a detectable viral load.[7] Three to five percent of syphilis cases in the United States develop neurological, ocular, or auditory complications, and the estimated rate of neurosyphilis is 0.47 to 2.1 per 100,000 individuals.[8] HIV is a major co-founder that tremendously increases the risk of developing neurosyphilis. Neurosyphilis is two times more common in men than in women and 2-3 times more common in Whites than Blacks, despite higher absolute rates of syphilis in blacks.[7,9] The United States has seen an increase in primary and secondary syphilis since 2000, consistent with global trends. Whereas in Nagaland, India, syphilis prevalence among female sex workers was found to be 21.1%, with 11.7% of them also testing positive for HIV.[10]

3 Pathogenesis

Although years may pass before neurological symptoms can be observed, *Treponema pallidum* enters the central nervous system (CNS) very early in syphilis. Pathogenesis directly affects the invasiveness of bacteria and the host immune response.[11] Although the majority of people can clear bacteria without any symptoms, for some, a chronic infection can persist and result in neurosyphilis, causing inflammation and neurological damage.[12] Neurosyphilis may present either early or late. Early neurosyphilis affects the meninges and blood vessels, causing diseases such as meningitis and stroke-like symptoms. In contrast, late neurosyphilis is typically characterized by inflammation associated with neuroinflammation and neurodegeneration in both the brain and the spinal cord.[3] *Treponema pallidum* enters the body from small abrasions in either the skin or other mucosal surfaces and can result in blood vessel damage and inflammation.[11,13] Early invasion of the CNS has been shown by research, and *T. pallidum* has been identified in the CSF of approximately 30% of patients with early syphilis. Others can clear the bacteria without any symptoms, but if unable to do so, they may develop neurosyphilis.[14]

4 Clinical Manifestations

4.1 Asymptomatic Neurosyphilis (Early Stage)[2,3]

- **Definition:** The most common type, which occurs before all other symptoms of syphilis, is seen in one-third of patients with neurosyphilis.
- **Diagnosis:** Positive CSF nontreponemal VDRL test; no neurological signs of syphilis, and primary or secondary syphilis may be present.
- **CSF Analysis:** Generally, a well-established abnormality of CSF is 5-100 WBC per microliter and a protein analysis indicates values of 45-100 mg/dL; major deviations can correlate with increased future risk for symptomatic neurosyphilis.

4.2 Meningeal Neurosyphilis (Early Stage)[2,3,15]

- **Characteristics:** This condition affects the vasculature and meninges, with positive cerebrospinal fluid (CSF) tests for VDRL and treponemal antibodies.
- **Manifestations:** Headaches, confusion, nausea, neck rigidity, cranial nerve deficits, seizures, and hydrocephalus can occur.
- **CSF**- Shows 200-400 WBCs/microL, protein 100-200 mg/dL; VDRL is always positive.

4.3 Meningovascular Neurosyphilis (Intermediate Stage)[3,16]

- **Definition:** Meningeal inflammation resulting in strokes, typically occurring after 5-12 years after infection.
- **Signs:** Strokes in younger adults, headache, dizziness, personality changes and potential symptoms affecting the spine
- **CSF:** 10–100 WBCs / μL; protein: 100–200 mg/dL; VDRL is typically positive.

4.4 Parenchymal Neurosyphilis (Late Stage)[3,17]

4.4.1 Syphilitic Paresis

- **Presentation:** dementia, personality changes with gradual onset 15-20 years after infection
- **Symptoms:** Restlessness, deterioration of cognitive functions, neurologic deficits, and Argyll Robertson pupil

- **CSF Result:** WBC Count 25-75 WBCs/microL; Protein 50-100 mg/dL; VDRL (almost always) positive

4.4.2 Tabes Dorsalis

- **Signs:** ataxic gait, stabbing pain, proprioception loss, and Argyll Robertson pupils.
- **CSF:** 50 WBC/μL, protein 45-75 mg/dL; VDRL, positive in ~75% of cases.

4.5 Other Considerations [18,19]

- **Ocular Syphilis:** It causes uveitis and vision loss and is often observed in HIV-positive patients.
- **Otosyphilis :** It is marked by sensorineural hearing loss and dizziness and is treated with penicillin.
- **Atypical Neurosyphilis:** These cases do not fit typical classifications and may present with symptoms resembling autoimmune disorders.

5 Diagnosis of Neurosyphilis

Diagnosing neurosyphilis is complex because of its varied presentations and the limitations of available tests. A comprehensive evaluation considers the medical features, symptoms, patient history, imaging studies, serological tests, and cerebrospinal fluid (CSF) analysis.

5.1 Clinical Evaluation

A thorough medical history, including a sexual history and any prior syphilis infection, is essential. Neurological examination is crucial for detecting focal deficits that could indicate neurosyphilis. [20]

5.2 Serologic Testing [21]

- Non-treponemal tests (e.g., VDRL and RPR): These tests are commonly used to screen for syphilis, but their sensitivity is limited when diagnosing neurosyphilis. However, they are also useful for tracking disease progression and monitoring treatment responses.
- Treponemal tests (e.g., FTA-ABS and TP-PA): These tests are more specific for detecting syphilis but cannot differentiate between active and previously treated infections. Positive results are expected in patients with neurosyphilis.

5.3 CSF Analysis is essential to confirm neurosyphilis

- **CSF VDRL:** A positive result strongly indicated neurosyphilis, although sensitivity was limited (up to 72%).
- **Elevated protein levels:** Protein levels above 50 mg/dL can support the diagnosis; however, this finding is nonspecific.
- **Pleocytosis:** A white blood cell counts of $\geq$20 cells/μL suggests neurosyphilis, whereas normal counts reduce the likelihood of diagnosis.
- **CSF FTA-ABS:** This test is sensitive for detecting neurosyphilis; however, the results may not always be specific.

5.4 Neuroimaging

MRI is the most sensitive technique for detecting neurosyphilis-related abnormalities such as cerebral infarcts, meningitis, or atrophy, depending on the stage of the disease. However, these findings are inconclusive, and neuroimaging is valuable for excluding other neurological conditions. [22]

6 Treatment

Central nervous system (CNS) involvement can occur at any stage of syphilis. CSF abnormalities are often detected early in syphilis, even in the absence of clinical neurological symptoms. If neurological issues such as cognitive dysfunction, deficits, or signs of meningitis are present, CSF examination should be performed before starting treatment. [2,3]

6.1 Ocular symptoms

Ocular symptoms such as uveitis and neuro retinitis can develop at any stage of syphilis. Patients with these symptoms and positive serology findings require thorough ocular examinations. CSF evaluation is necessary in the presence of cranial nerve dysfunction. However, for isolated ocular symptoms without cranial nerve involvement, CSF examination is not required before treatment. Prompt referral to an ophthalmologist is crucial, and ocular syphilis should be treated as neurosyphilis regardless of CSF findings. [23]

6.2 Otosyphilis

Hearing loss can occur at any stage of syphilis and may involve cranial nerves VIII. In isolated cases where neurological examinations are normal, CSF examination is generally not required before treatment. Management should include referral to an otolaryngologist, and treatment should follow the same approach as that for neurosyphilis. [24]

6.3 Recommended Treatment Regimen [25]

- **First-line treatment:** Aqueous crystalline penicillin G: 18–24 million units per day (administered as 3–4 million units IV every 4 h) for 10–14 days.
- **Alternative Treatment:** Procaine penicillin G: 2.4 million units IM daily, combined with probenecid: 500 mg orally four times a day for 10–14 days.
- **Extended Treatment:** Consider using benzathine penicillin: 2.4 million units IM weekly for 1–3 weeks after

completing the neurosyphilis regimen to extend the overall treatment duration.

6.4 Additional Management Considerations[26]

- All patients should undergo HIV testing, and those who test negative should be offered PrEP.
- Although systemic steroids can be used occasionally, their benefits are not well established.
- Follow-up: Normalization of serum RPR serves as a reliable indicator of improvement in abnormal CSF parameters, eliminating the need for repeated CSF examinations in stable patients.

Special Considerations

- **Penicillin Allergy**: If concerns regarding ceftriaxone, typically administered at a dose of 1–2 g daily for 10–14 days, skin testing for penicillin allergy is recommended as an alternative.
- **Pregnancy**: Pregnant women with a penicillin allergy should undergo desensitization and treatment with penicillin G.
- **HIV Infection**: The treatment protocol for neurosyphilis in HIV-positive patients is the same as that for HIV-negative individuals.[27]

7 Prognosis

The prognosis for neurosyphilis depends on the timing of diagnosis and treatment. Early detection and effective treatment can prevent major neurological damage and often result in a full recovery. However, in late-stage neurosyphilis, especially in cases involving general paresis or Tabes dorsalis, some neurological damage may be irreversible.[28]

7.1 Treatment Outcomes

While penicillin is effective in eradicating infections, neurological problems, especially in advanced cases, may persist even after treatment. HIV-positive patients typically have a worse prognosis, particularly those with a compromised immune system.[3]

7.2 Relapse and Long-term Follow-up

After treatment, follow-up care involved repeat CSF testing at 6 and 12 months. Persistent CSF abnormalities may indicate ineffective treatment or relapse, necessitating further treatment.[3]

8 Discussion

Neurosyphilis poses considerable challenges in diagnosis and treatment, owing to its diverse clinical presentations and complications from HIV co-infection. Overlapping symptoms with other CNS disorders can result in misdiagnosis or delayed diagnosis, thereby increasing the risk of lasting neurological damage.[3,29] The increasing rate of syphilis, especially among men who have sex with men (MSM) and individuals living with HIV (PLWH), highlights the importance of focused screening. If left untreated, neurosyphilis can cause serious complications, with increasing cases noted in younger patients with ischemic stroke. However, care must be taken to prevent stigmatization, which can deter individuals from seeking treatment.[30] Although managing neurosyphilis is more challenging with HIV coinfection, patient outcomes are typically comparable to those without HIV infection. Treating neurosyphilis is challenging because of the absence of in vitro cultures for *Treponema pallidum*, frequent false negatives and positives in diagnostic tests, and limited options for patients allergic to penicillin or ceftriaxone.[31] The serofast phenomenon complicates follow-up and lumbar punctures carry inherent risks. Delays in treatment are common because many patients are unaware of early syphilis symptoms.[1] Effective management involves balancing public education, partner notification, and screening efforts while reducing stigma. Although prophylactic treatment for partners is not recommended, serological testing is essential to assess the transmission risk.[32] Future research should focus on improving the diagnostic tools, identifying specific biomarkers for early neu-

Table 1. Diagnostic criteria or treatment regimens for different stages of neurosyphilis

Stage of Neurosyphilis	Diagnostic Criteria	Treatment Regimen
Early Neurosyphilis (within 1 year of infection)	- Positive serology (e.g., VDRL, FTA-ABS) - CSF analysis showing elevated WBC count, increased protein, and positive CSF VDRL	- Penicillin G (IV) 3–4 million units every 4 hours for 10–14 days
Late Neurosyphilis (after 1 year of infection)	- History of untreated syphilis - Positive serological tests - CSF analysis showing elevated WBC count and increased protein	- Penicillin G (IV) 3–4 million units every 4 hours for 10–14 days
Tertiary Neurosyphilis (including general paresis and tabes dorsalis)	- Clinical features: cognitive decline, motor dysfunction, or sensory loss - Serological tests for syphilis - MRI/CT findings suggestive of brain involvement	- Penicillin G (IV) 3–4 million units every 4 hours for 10–14 days

rosyphilis, and developing tailored treatment standards and prevention strategies for MSM and PLWH.[33]

9 Conclusion

Neurosyphilis poses major challenges, especially among men who have sex with men (MSM) and those living with HIV (PLWH). Key issues include misdiagnosis and treatment delays, underscoring the importance of targeted screening and public health efforts to raise awareness and reduce stigma. Accurate diagnosis of neurosyphilis relies on thorough clinical evaluation and cerebrospinal fluid analysis, with penicillin as the standard treatment. However, challenges such as penicillin allergies and the serofast phenomenon necessitate alternative approaches and careful follow-ups. Future research should focus on the development of more sensitive diagnostic tools and innovative treatment methods tailored to at-risk populations. A comprehensive approach could improve the outcomes for individuals affected by this re-emerging disease.

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