Section: DVL

Original Research Article

NEURAL INVOLVEMENT IN LATENT SYPHILIS

Deepthi Vijayakumar[1], B. Jayalakshmi Dhevi[2], S. Kalpanadevi[3]

[1]Senior Assistant Professor, Department of Dermatology, Venerology & Leprosy, Government Rajaji Hospital & Madurai Medical College, Tamilnadu, India.
[2]Senior Resident, Department of Dermatology, Venerology & Leprosy, Government Rajaji Hospital & Madurai Medical College, Tamilnadu, India.
[3]Junior Resident, Department of Dermatology, Venerology & Leprosy, Government Rajaji Hospital & Madurai Medical College, Tamilnadu, India.

Received : 10/07/2025
Received in revised form : 12/08/2025
Accepted : 03/09/2025

Keywords:
Latent syphilis, Neural involvement, Cerebrospinal fluid, VDRL, TPHA, Behavioural risk factors.

Corresponding Author:
Dr. Deepthi Vijayakumar,
Email: dr.deepthivijayakumar@gmail.com

DOI: 10.47009/jamp.2025.7.5.82

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (5); 414-418

ABSTRACT

Background: Latent syphilis is a stage in which infection is confirmed by serological tests without clinical symptoms. Neural involvement can occur silently at this stage, leading to serious complications if left untreated. Early detection through cerebrospinal fluid (CSF) examination may help in the timely intervention and prevention of neurological diseases. **Objective:** To assess the pattern and prevalence of neural involvement in latent syphilis using CSF parameters, including VDRL, TPHA, cell count, protein, and sugar levels. **Materials and Methods:** A prospective observational study was conducted on 30 patients with late latent syphilis or syphilis of unknown duration who attended a tertiary care hospital. A detailed history, examination, and serological screening were performed. Lumbar puncture was performed under aseptic precautions, and CSF was analysed for VDRL, TPHA, protein, sugar, and cell count. **Result:** Most patients were male (83.33%) and in the 31–40 years' age group (46.67%). Late latent syphilis was present in 36% of patients, and syphilis of unknown duration in 64% of patients. Asymptomatic cases accounted for 86.67% of the total, while 13.33% had genital complaints. Multiple sexual partners were reported by 46.67% of the patients, and 83.33% did not use condoms. All CSF VDRL and TPHA tests were negative, with a mean CSF protein of 35.45 mg/dl, a mean sugar of 51.64 mg/dl, and a mean cell count of 7 cells/mm³. HIV was non-reactive in all the patients. **Conclusion:** Most patients with latent syphilis were asymptomatic, but behavioural risks were common, favouring disease transmission. Although standard CSF tests were negative, the analysis of parameters such as CSF-TPPA can aid in detecting silent neural involvement.

INTRODUCTION

Treponema pallidum is a spirochete that causes syphilis, a chronic sexually transmitted infection.[1] It is a systemic disease that can affect several organs over time.[2] Obliterative endarteritis is the main pathological change that can cause tissue damage in the central nervous system (CNS) and other systems.[3] The disease progresses through primary, secondary, latent, and tertiary clinical stages.[4] Positive serological tests without clinical symptoms indicate latent syphilis. It is divided into two categories: late latent (infection of unknown onset or longer duration) and early latent (infection within the previous year).[5]

Any stage of syphilis can involve the brain.[6] Within weeks of the initial infection, Treponema pallidum can infiltrate the central nervous system and, if untreated, persist for years.[7] This is known as asymptomatic neurosyphilis when it occurs without neurological symptoms or signs. Although clinically silent, it may progress to symptomatic neurosyphilis, presenting as tabes dorsalis, meningitis, stroke, sensory deficits, or mental disorders.[8]

In latent syphilis, neurological evaluation is often not routine because the patients appear clinically normal. However, certain laboratory parameters can help in the early identification of CNS invasion. Examination of cerebrospinal fluid (CSF) remains the cornerstone for diagnosing asymptomatic neurosyphilis.[9] Key indicators include elevated CSF mononuclear cell count (pleocytosis), increased total protein concentration, and reactive non-treponemal or treponemal tests in CSF.[10] The Venereal Disease Research Laboratory (VDRL) test in CSF is highly specific but less sensitive, whereas the Treponema pallidum haemagglutination assay (TPHA) in CSF is more sensitive but less specific. Other parameters, such as CSF sugar levels, may provide supportive information in specific contexts.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Neurosyphilis can occur in both HIV-infected and non-HIV-infected individuals, but the prevalence and pattern may vary depending on host immunity, duration of infection, and treatment history.6 In latent syphilis, especially in late latent cases, CNS involvement may already be present despite the absence of symptoms.[8] Studies suggest that a proportion of such patients have abnormal CSF findings, emphasising the importance of systematic evaluation to detect silent disease.[9]

Understanding the patterns and prevalence of neural involvement in latent syphilis is crucial for guiding clinical practice. It assists in determining which patients require lumbar punctures, initiating appropriate antibiotics, and monitoring treatment outcomes. Additionally, recording CSF abnormalities can help create evidence-based screening guidelines for latent syphilis.[10] To improve the early detection and prevention of neurological complications, the current study aimed to identify the pattern and prevalence of neural involvement in patients with latent syphilis and assess CSF parameters, including VDRL, TPHA, cell count, protein, and sugar levels.

MATERIALS AND METHODS

This prospective observational study included 30 patients with late-stage syphilis who attended the Venereology Outpatient Department of Government Rajaji Hospital, Madurai. The study was conducted at the Department of Dermatology, Madurai Medical College, and Government Rajaji Hospital, Tamil Nadu, for 14 months from July 2023 to September 2024. Approval was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrolment.

Inclusion Criteria

Individuals aged ≥ 18 years diagnosed with late-stage or unknown-duration syphilis were included. Enrolment was limited to those who provided informed consent and agreed to follow-up visits.

Exclusion Criteria

Pregnant or lactating women, individuals aged < 18 years, and patients with focal neurological deficits, elevated intracranial pressure, or a history of head trauma were excluded from the study. Patients with coagulation disorders, HIV/AIDS, on immunosuppressive therapy, or with systemic or local infection at the lumbar puncture site were also excluded from the study.

Methods

A thorough history and physical examination were performed for each patient. Serological tests, including the Treponema pallidum haemagglutination assay (TPHA) and Rapid Plasma Reagin (RPR) test, were used to screen for syphilis. Patients with latent syphilis who tested positive were included in the study. Baseline investigations after admission included complete blood count, random blood sugar, liver and kidney function tests, HIV and hepatitis B and C serology, chest X-ray, electrocardiogram, and echocardiogram. Under strict aseptic precautions and with the assistance of an anaesthetist, a lumbar puncture was performed. CSF samples were collected and sent for laboratory analysis, including CSF VDRL, CSF TPHA, protein estimation, cell count, and sugar levels, to evaluate possible neural involvement.

Statistical Analysis

The collected data were analysed using IBM SPSS Statistics v27. Descriptive statistics were used to summarise categorical variables, which were expressed as frequencies and percentages with 95% confidence intervals.

RESULTS

Patients ranged from under 20 to over 50 years of age, with the largest proportion belonging to the 31–40 years age group (46.6%, 95% CI: 28.34–65.67). The 21–30 years' group accounted for 26.6% (95% CI: 12.28–45.89), while 13.3% (95% CI: 3.76–30.72) were aged ≤ 20 years, 10% (95% CI: 2.11–26.53) were aged 41–50 years, and only 3.3% (95% CI: 0.08–17.22) were above 50 years. Males formed the majority at 83.3% (95% CI: 65.28–94.36), with females comprising 16.6% (95% CI: 5.64–34.72). Regarding marital status, 53.3% (95% CI: 34.33–71.66) were married and 46.6% (95% CI: 28.34–65.67) were unmarried (Table 1).

Table 1: Demographic distribution of study patients

Variable		N (%)	95% CI	
			Lower	Upper
Age group (years)	≤ 20	4 (13.3%)	3.76	30.72
	21–30	8 (26.6%)	12.28	45.89
	31–40	14 (46.6%)	28.34	65.67
	41–50	3 (10%)	2.11	26.53
	> 50	1 (3.3%)	0.08	17.22
Gender	Female	5 (16.6%)	5.64	34.72
	Male	25 (83.3%)	65.28	94.36
Marital status	Unmarried	14 (46.6%)	28.34	65.67
	Married	16 (53.3%)	34.33	71.66

Heterosexual orientation was the most common (60%, 95% CI: 40.60–77.34), followed by homosexual orientation (30%, 95% CI: 14.73–49.40), while 6.6% (95% CI: 0.82–22.07) identified as bisexual and 3.3% (95% CI: 0.08–17.22) reported no sexual exposure. Nearly half of the patients

ISSN (O): 2687-5365; ISSN (P): 2753-6556

(46.6%, 95% CI: 28.34–65.67) had multiple partners, 33.3% (95% CI: 17.29–52.81) reported only marital contact, and 20% (95% CI: 7.71–38.57) had a single partner. Recent sexual exposure of less than one year was reported by 62% (95% CI: 42.26–79.31), whereas 37.9% (95% CI: 20.69–57.74) had exposure for one year or more. Barrier protection was not used by 83.3% (95% CI: 65.28–94.36), while 13.3% (95% CI: 3.76–30.72) used it occasionally, and only 3.3% (95% CI: 0.08–17.22) reported its consistent use (Table 2).

Table 2: Sexual behaviour profile

Variable		N (%)	95% CI	
			Lower	Upper
Sexual orientation	Bisexual	2 (6.6%)	0.82	22.07
	Heterosexual	18 (60%)	40.6	77.34
	Homosexual	9 (30%)	14.73	49.4
	No exposure history	1 (3.3%)	0.08	17.22
Number of partners	Only marital contact	10 (33.3%)	17.29	52.81
	Single	6 (20%)	7.71	38.57
	Multiple	14 (46.6%)	28.34	65.67
Sexual activity duration	< 1 year (Recent)	18 (62%)	42.26	79.31
	≥ 1 year (Remote)	11 (37.9%)	20.69	57.74
Barrier protection use	No	25 (83.3%)	65.28	94.36
	Occasionally	4 (13.3%)	3.76	30.72
	Yes	1 (3.3%)	0.08	17.22

Most patients (86.6%, 95% CI: 69.28–96.24) reported no complaints, whereas 13.3% (95% CI: 3.76–30.72) presented with genital Regarding substance use, 46.6% (95% CI: 28.34–65.67) reported both smoking and alcohol consumption, 33.3% (95% CI: 17.29–52.81) reported no substance use, 13.3% (95% CI: 3.76–30.72) were smokers, and 6.6% (95% CI: 0.82–22.07) consumed alcohol only. Among the 16 married patients, 25% were seroconcordant and 75% were serodiscordant couples (Table 3).

Table 3: Clinical complaints, substance use, and seroconcordance status

Variable		N (%)	95% CI	
			Lower	Upper
Complaints	None	26 (86.6%)	69.28	96.24
	Genital complaints	4 (13.3%)	3.76	30.72
Substance abuse	None	10 (33.3%)	17.29	52.81
	Smoker	4 (13.3%)	3.76	30.72
	Alcoholic	2 (6.6%)	0.82	22.07
	Both	14 (46.6%)	28.34	65.67

All patients had normal general, systemic, and vital examinations (100%, 95% CI: 88.43–100). Genital examination was normal in 28 (93.3%, 95% CI: 62.10–98.66), with 2 (6.6%, 95% CI: 0.82–22.07) showing positive findings. HIV was non-reactive in all cases. RPR titres were non-reactive in 18 (60%, 95% CI: 40.60–77.34), 1:2 in 9 (30%, 95% CI: 14.73–49.40), 1:4 in 2 (6.67%, 95% CI: 0.82–22.07), and 1:8 in 1 (3.3%, 95% CI: 0.08–17.22), while TPHA was positive in all (100%, 95% CI: 88.43–100). Late latent syphilis was diagnosed in 11 (36%, 95% CI: 28.60–52.00) and syphilis of unknown duration in 19 (64%, 95% CI: 48.44–79.40) patients. CSF analysis showed a mean cell count of 7 (median 3, range 2–80), mean protein of 35.45 mg/dl (median 31.5, range 14–125), and mean sugar of 51.64 mg/dl (median 50, range 28–75), with all CSF VDRL and TPHA negative (100%, 95% CI: 88.43–100) (Table 4).

Table 4: Clinical, serological, and cerebrospinal fluid findings

Variable		N (%)	95% CI	
			Lower	Upper
Genital examination	Normal	28 (93.3%)	62.1	98.66
	Positive findings	2 (6.6%)	0.82	22.07
HIV status	Non-reactive	30 (100%)	88.43	100
RPR titre	Non-reactive	18 (60%)	40.6	77.34
	01:02	9 (30%)	14.73	49.4
	01:04	2 (6.6%)	0.82	22.07
	01:08	1 (3.3%)	0.08	17.22
TPHA	Positive (all)	30 (100%)	88.43	100
Diagnosis	Late latent syphilis	11 (36%)	28.6	52
	Syphilis of unknown duration	19 (64%)	48.44	79.4
CSF VDRL	Negative	(30, 100%)	88.43%	100%
CSF TPHA	Negative	(30, 100%)	88.43%	100%

ISSN (O): 2687-5365; ISSN (P): 2753-6556

DISCUSSION

Our study examined the demographic, behavioural, and laboratory characteristics of patients diagnosed with syphilis. The study population ranged from under 20 to over 50 years, with most patients aged 31–40. The majority were male, and slightly more than half were married. Similarly, Clarkson-During et al., in a study involving 171 patients with syphilis, reported that individuals aged 50 years and above accounted for 50.3% of cases, followed by the 30–39 years' age group at 20.5%. The majority of patients were males, comprising 61.9% of the study population.[11] Lakshminarayan et al. found that among 58 patients diagnosed with syphilis, 48 (82.75%) were married, 6 (10.34%) were unmarried, and 4 (6.89%) were divorced.[12] Syphilis in this study predominantly affected middle-aged married men, consistent with earlier findings that emphasised demographic factors influencing disease distribution.
In our study, heterosexual orientation was the most frequent (60%), with multiple sexual partners reported by 46.67% and sexual exposure under one year by 62.07%. Barrier protection was largely absent (83.33%), while occasional and consistent use was reported by 13.33% and 3.33% of the participants, respectively. Similarly, Marques et al. reported that the majority were heterosexual (91.62%) and single-partnered (68.54%), while homosexual orientation (8.38%) and multiple partners (31.46%) were linked to a higher infection risk (OR: 2.93 and 1.82, respectively). Condom use varied, with 62.20% of participants not using condoms with steady partners, and consistent use was significantly associated with protection (OR: 2.2, 95% CI: 1.57–3.05).13 Rushmore et al. found that 91.62% of participants were heterosexual, 8.38% were homosexual, and 68.54% had a single partner, while 62.20% did not use condoms with steady partners, and 43.97% used them consistently with casual partners.[14] The findings indicate that heterosexual orientation predominated, with risky behaviours such as multiple partners and inconsistent condom use significantly influencing syphilis transmission.
Our study showed that most patients were asymptomatic, a few had genital complaints, some reported substance use, and others did not report substance use. Among married couples, one-quarter were seroconcordant and the remainder were serodiscordant. Similarly, Orlova et al. reported that among 400 patients, including 100 with neurosyphilis, most had no complaints (86.67%), while 13.33% presented with genital symptoms; 46.67% reported both smoking and alcohol use, and 33.33% reported no substance use. Among married patients, 25% were seroconcordant and 75% were serodiscordant couples.[15] This shows that most patients were asymptomatic, with limited complaints, variable substance use, and predominantly serodiscordant status among married couples.
In our study, HIV was non-reactive in all patients, RPR titres varied among patients, and TPHA was positive in all cases. Similarly, Burchell et al. found that among men who have sex with men (MSM), the annual prevalence of reactive syphilis tests with high RPR titres (≥1:16) reached a peak of 3.8%.[16] Gupta et al. reported that TPHA was positive in all participants (100%, 95% CI: 88.43–100), while VDRL showed low-titre reactivity in the sera.[17] This indicates that universal TPHA positivity with variable RPR titres is consistent with previous findings highlighting treponemal test reliability in syphilis detection.
Our study showed that late latent syphilis was identified in 36% (95% CI: 28.60–52.00) of cases. Syphilis of unknown duration accounted for 64% (95% CI: 48.44–79.40). Similarly, Girma and Amogne reported that among HIV-experienced individuals, 3.8% were diagnosed with latent syphilis, of which 71% were classified as late latent.18 Mangone et al. found that 42.9% of individuals were diagnosed with late latent or syphilis of unknown duration.[19] A higher proportion of syphilis cases of unknown duration was observed compared to late latent cases, which is consistent with previous epidemiological observations.
Our study shows that a CSF-TPPA titre of ≥1:320 is a sensitive and practical marker for diagnosing neurosyphilis, providing a reliable alternative to CSF-VDRL results are negative. Similarly, Shi et al. reported that a CSF-TPPA titre of ≥1:320 is a sensitive and practical marker for diagnosing neurosyphilis, providing a reliable alternative when CSF-VDRL results are negative.[20] Dharmasaroja et al. found that most symptomatic patients (85.7%) had elevated CSF WBCs (>20 cells/mm³) with a mean of 98.6 ± 136.0 compared to 3.2 ± 7.3 in non-neurosyphilitic patients.[21] This study supports CSF-TPPA ≥1:320 as a reliable marker for neurosyphilis, particularly when CSF-VDRL is negative, corroborating prior research.
Our study highlights syphilis across diverse ages, mainly in males, often asymptomatic, with late latent cases being common. Behavioural risks, including multiple partners and low condom use, promote transmission. CSF-TPPA is an effective diagnostic tool for neurosyphilis when standard tests fail to detect the disease.

Limitations

The study was limited by its small sample size from a single tertiary care centre, which may reduce the generalisability of the findings. The absence of long-term follow-up data restricted the assessment of the progression to symptomatic neurosyphilis. Additionally, reliance on routine CSF parameters without advanced molecular tests may have led to an underestimation of early or subclinical neural involvement.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

CONCLUSION

Our study showed that most patients with latent syphilis had no symptoms, with late cases being more frequent. Males were the majority, and many reported multiple sexual partners with low condom use, which increased the risk of transmission. Standard CSF tests, including VDRL and TPHA, were negative in all cases; however, CSF-TPPA showed potential in detecting neural involvement when routine methods were negative. These findings highlight the importance of screening selected patients for silent neurological diseases, even without visible signs, to prevent disease progression. Early identification through appropriate CSF analysis can guide timely treatment and reduce the risk of serious neurological problems.

REFERENCES

1. Nair PS. Frequency of asymptomatic neurosyphilis in patients with latent syphilis: A 4-year retrospective study from a tertiary care centre. J Skin Sex Transm Dis 2024; 6:54–6. https://doi.org/10.25259/jsstd_67_2023.
2. Carlson JA, Dabiri G, Cribier B, Sell S. The immunopathobiology of syphilis: the manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. Am J Dermatopathol 2011; 33:433–60. https://doi.org/10.1097/DAD.0b013e3181e8b587.
3. Munshi S, Raghunathan SK, Lindeman I, Shetty AK. Meningovascular syphilis causing recurrent stroke and diagnostic difficulties: a scourge from the past. BMJ Case Rep 2018;2018: bcr-2018-225255. https://doi.org/10.1136/bcr-2018-225255.
4. Tudor ME, Al Aboud AM, Leslie SW, Gossman W. Syphilis. Stat Pearls, Treasure Island (FL): Stat Pearls Publishing; 2025. https://www.ncbi.nlm.nih.gov/books/NBK534780/.
5. Tiecco G, Degli Antoni M, Storti S, Marchese V, Focà E, Torti C, et al. A 2021 update on syphilis: Taking stock from pathogenesis to vaccines. Pathogens 2021; 10:1364. https://doi.org/10.3390/pathogens10111364.
6. Ha T, Tadi P, Leslie SW, Dubensky L. Neurosyphilis. StatPearls, Treasure Island (FL): StatPearls Publishing; 2025. https://www.ncbi.nlm.nih.gov/books/NBK540979/.
7. Hamill MM, Ghanem KG, Tuddenham S. State-of-the-art review: Neurosyphilis. Clin Infect Dis 2024;78: e57–68. https://doi.org/10.1093/cid/ciad437.
8. Zhou J, Zhang H, Tang K, Liu R, Li J. An updated review of recent advances in neurosyphilis. Front Med (Lausanne) 2022; 9:800383. https://doi.org/10.3389/fmed.2022.800383.
9. Li W, Han J, Zhao P, Wang D, Sun T, Guo J, et al. Predicting asymptomatic neurosyphilis using peripheral blood indicators. BMC Infect Dis 2021; 21:1191. https://doi.org/10.1186/s12879-021-06846-6.
10. Wang Y-Y, Shi M, Guan Z-F, Zhang L, Gu X, Lu H-K, et al. Clinical features and corrected factors with neurosyphilis in HIV/syphilis co-infected patients based on the stage of syphilis. Int J Dermatol Venereol 2022; 5:61–7. https://doi.org/10.1097/jd9.0000000000000219.
11. Clarkson-During A, Almirol E, Eller D, Hazra A, Stanford KA. Risk factors for treatment non-completion among patients with syphilis. Ther Adv Infect Dis 2024; 11:20499361241265941. https://doi.org/10.1177/20499361241265941.
12. Lakshminarayan D, Vodapalli AK, Kolla SH, Nakka AR. Seroprevalence of syphilis in human immunodeficiency virus patients with special reference to diagnostic utility of rapid plasma reagin test. MRIMS J Health Sci 2023; 11:234–8. https://doi.org/10.4103/mjhs.mjhs_80_22.
13. Marques CC, Mariz FN de C, Marques TC, Rohr JTD, Moreira B, Santiago PB, et al. Risk factors associated with syphilis among patients at a sexual health centre in Brazil: A retrospective study. Braz J Infect Dis 2025; 29:104558. https://doi.org/10.1016/j.bjid.2025.104558.
14. Rushmore J, Jackson DA, Grey JA, Torrone EA, Learner ER. Assessing alignment of sexual orientation and sex of sex partners among men with primary and secondary syphilis, 2022. Sex Transm Dis 2025. https://doi.org/10.1097/OLQ.0000000000002213.
15. Orlova E, Gadaev I, Smirnova L, Kolenko N, Zykova E. Clinical and laboratory characteristics of neurosyphilis: analysis of symptoms and risk factors. Eur J Med Res 2025; 30:139. https://doi.org/10.1186/s40001-025-02349-1.
16. Burchell AN, Allen VG, Moravan V, Gardner S, Raboud J, Tan DHS, et al. Patterns of syphilis testing in a large cohort of HIV patients in Ontario, Canada, 2000-2009. BMC Infect Dis 2013; 13:246. https://doi.org/10.1186/1471-2334-13-246.
17. Gupta K, Bhardwaj A, Dash S, Kaur IR. Role of Treponema pallidum hemagglutination assay for diagnosis of syphilis in low titers of VDRL-reactive sera: A prospective study from a large tertiary care centre of East Delhi. J Family Med Prim Care 2018; 7:1594–5. https://doi.org/10.4103/jfmpc.jfmpc_258_18.
18. Girma S, Amogne W. Investigating latent syphilis in HIV treatment-experienced Ethiopians and response to therapy. PLoS One 2022;17: e0270878. https://doi.org/10.1371/journal.pone.0270878.
19. Mangone E, Bell J, Khurana R, Taylor MM. Treatment completion with a three-dose series of benzathine penicillin among people diagnosed with late latent and unknown duration syphilis, Maricopa County, Arizona. Sex Transm Dis 2023; 50:298–303. https://doi.org/10.1097/OLQ.0000000000001775.
20. Shi M, Long F, Zou D, Gu X, Ni L, Cheng Y, et al. Evaluation of cerebrospinal fluid treponema pallidum particle agglutination assay titer for neurosyphilis diagnosis among HIV-negative syphilis patients. Front Immunol 2025; 16:1572137. https://doi.org/10.3389/fimmu.2025.1572137.
21. Dharmasaroja PA, Dharmasaroja P. Serum and cerebrospinal fluid profiles for syphilis in Thai patients with acute ischaemic stroke. Int J Std Aids 2012; 23:340–5. https://doi.org/10.1258/ijsa.2011.011207.

ISSN (O): 2687-5365; ISSN (P): 2753-6556