

Clinical and laboratory factors associated with neurosyphilis and the diagnostic performance of cerebrospinal fluid markers: a retrospective observational study

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Abstract

Background

Neurosyphilis can occur at any stage of syphilis, but no universally accepted diagnostic gold standard exists. This study evaluated clinical and laboratory factors associated with neurosyphilis and assessed the discriminative performance of selected serum and cerebrospinal fluid indicators.

Methods

This retrospective observational study included 281 patients with syphilis who underwent cerebrospinal fluid examination at the First and Second Affiliated Hospitals of Anhui Medical University between August 2020 and August 2024. Patients were classified as having neurosyphilis (NS) or non-neurosyphilis (NNS) according to the Chinese guideline-based diagnostic criteria used in the study. Demographic, serum, and cerebrospinal fluid variables were compared between groups. Multivariable binary logistic regression was used to evaluate variables associated with NS, and receiver operating characteristic curve analysis was used to assess diagnostic discrimination.

Results

Of the 281 patients, 86 had NS and 195 had NNS. Patients with NS were older and more frequently male than patients with NNS. Serum glucose and several cerebrospinal fluid variables differed significantly between groups. In the multivariable model, age, serum glucose, cerebrospinal fluid albumin, cerebrospinal fluid white blood cell count, cerebrospinal fluid IgG, Pandy's test, and the cerebrospinal fluid/serum albumin quotient were significantly associated with NS, whereas serum creatinine was not statistically significant. Cerebrospinal fluid IgG showed the highest discriminative performance among the evaluated indicators (AUC 0.902, 95% CI 0.856–0.948). At a cutoff value of 54.7, its sensitivity was 79.2% and specificity was 91.0%.

Conclusions

Several clinical and cerebrospinal fluid variables were associated with neurosyphilis in this retrospective observational study of patients with syphilis undergoing cerebrospinal fluid examination. Cerebrospinal fluid IgG showed the highest individual discriminative performance and may provide useful adjunctive information when evaluating possible neurosyphilis. Independent validation is warranted.

Background

Neurosyphilis (NS) is an infection of the nervous system caused by *Treponema pallidum* and can occur at any stage of syphilis [1]. Delayed recognition and treatment may lead to substantial neurological

morbidity. Although serological testing is well established for the diagnosis of syphilis, the diagnosis of neurosyphilis remains challenging because there is no universally accepted single diagnostic gold standard and diagnostic criteria vary across settings.

Contemporary studies have continued to examine host factors, cerebrospinal fluid (CSF) abnormalities, and intrathecal immune responses that may aid the assessment of neurosyphilis [3–5]. CSF pleocytosis and elevated protein concentrations are commonly incorporated into diagnostic frameworks, while CSF immunoglobulin measurements and other biomarkers may provide additional information [4, 8, 9]. The clinical value of routinely available laboratory indicators therefore remains of practical interest, particularly when more specialized testing is unavailable.

This study retrospectively analyzed demographic characteristics and serum and CSF laboratory findings from 281 patients with syphilis who underwent CSF examination at two affiliated hospitals between August 2020 and August 2024. The aim was to identify factors associated with neurosyphilis and to evaluate the discriminative performance of selected routinely available indicators.

Methods

Study design and setting

This retrospective observational study included patients with syphilis who underwent CSF examination at the First and Second Affiliated Hospitals of Anhui Medical University between August 2020 and August 2024. Clinical and laboratory data were obtained from the electronic medical record systems. For patients with multiple eligible encounters and an unchanged diagnosis, only data from the first eligible encounter were included.

Participants

A total of 281 eligible patients with syphilis, aged 16–76 years, were included. Demographic and clinical information included sex, age, clinical manifestations, and HIV infection status, together with relevant serum and CSF laboratory findings. Patients were excluded if they had confirmed HIV infection, pregnancy, other conditions that could cause CSF abnormalities, contraindications to lumbar puncture, severe infections involving vital organs, or refusal to participate in the study.

Definition of neurosyphilis

Neurosyphilis was defined according to the Chinese Guidelines for the Diagnosis and Treatment of Syphilis, Gonorrhea and Genital Chlamydia trachomatis Infection (2020) [6]. Patients were classified as having NS if they had CSF abnormalities, defined as elevated CSF protein (> 0.5 g/L) and/or a leukocyte count of at least 5×10^6 /L, together with positive serum toluidine red unheated serum test (TRUST) and *Treponema pallidum* particle agglutination assay (TPPA) results in the absence of another identifiable

cause of the CSF abnormalities, or if the CSF TRUST result was reactive. Patients with syphilis who did not meet the diagnostic criteria for NS were classified into the non-neurosyphilis (NNS) group.

Data collection and laboratory variables

Demographic, clinical, and laboratory data were obtained from the medical records. Serum variables evaluated in the study included glucose, immunoglobulin G (IgG), chloride, total bilirubin, alanine aminotransferase (ALT), creatinine, and total protein. CSF variables included Pandy's test, albumin, glucose, white blood cell (WBC) count, chloride, and IgG. The CSF/serum albumin quotient (Qalb) was included among the evaluated CSF-related variables.

Statistical analysis

Case information was collated using Microsoft Excel 2007, and statistical analyses were performed using SPSS version 27.0. The Shapiro–Wilk test was used to assess the distribution of continuous variables. Continuous variables that were not normally distributed were presented as medians with the 25th and 75th percentiles and compared between the NS and NNS groups using the Mann–Whitney U test. Categorical variables were presented as numbers and percentages and compared using the chi-square test. Multivariable binary logistic regression with a forward stepwise method was performed to evaluate factors associated with neurosyphilis. The model included age, serum glucose, serum creatinine, CSF albumin, CSF WBC count, CSF IgG, Pandy's test, and Qalb. Regression coefficients (β), standard errors (SEs), Wald χ^2 statistics, odds ratios (ORs), 95% confidence intervals (CIs), and P values were reported. Regression coefficients, standard errors, odds ratios (ORs), 95% confidence intervals (CIs), and P values were reported. Because some variables contained missing observations, cases with missing values required for a given analysis were excluded from that analysis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative performance of selected clinical and laboratory indicators for NS. Discriminative performance was quantified using the area under the ROC curve (AUC) with 95% CIs. The optimal cutoff for CSF IgG was determined by maximizing the Youden index (sensitivity + specificity – 1). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study population

A total of 281 patients with syphilis were included, of whom 86 were classified as having NS and 195 as NNS. Patients in the NS group were older than those in the NNS group, with median ages of 51.00 years (36.50, 58.25) and 35.00 years (26.00, 55.00), respectively ($P < 0.001$). The proportion of male patients was significantly higher in the NS group than in the NNS group [66 (76.74%) vs. 74 (37.95%), $P < 0.001$] (Table 1).

Table 1
Characteristics of the study population

Age, years	NS (n = 86)	NNS (n = 195)	χ^2/Z	P value
	51.00 (36.50, 58.25)	35.00 (26.00, 55.00)	-4.502	< 0.001
Male, n (%)	66 (76.74%)	74 (37.95%)		
Female, n (%)	20 (23.26%)	121 (62.05%)	35.930	< 0.001
Serum parameters				
Serum glucose (mmol/L)	5.17 (4.81,6.07)	4.76 (4.39,5.12)	-3.101	0.002
Serum IgG	11.46 (9.27,12.77)	11.27 (9.74,12.96)	-0.094	0.094
Serum chloride	105.25 (103.85,107.18)	106.00 (104.00,107.00)	-0.857	0.392
Serum total bilirubin	12.91 (8.91,17.59)	10.60 (8.36,13.50)	-2.637	0.008
Serum ALT	19.00 (13.75,31.00)	15.00 (11.00,23.00)	-2.311	0.021
Serum creatinine	59.05 (49.98,68.50)	52.90 (45.80,64.20)	-4.670	< 0.001
CSF parameters				
Pandy's test positive, n (%)	43 (50.00%)	7 (3.60%)	86.520	< 0.001
CSF albumin (g/L)	0.60 (0.46,0.74)	0.32 (0.25,0.40)	-9.705	< 0.001
CSF glucose (mmol/L)	3.47 (3.13,4.04)	3.39 (3.17,3.67)	-1.872	0.061
CSF WBC count ($\times 10^6/L$)	7.50 (3.00,36.50)	1.00 (1.00,3.00)	-8.768	< 0.001
CSF chloride	124.85 (122.76,125.63)	123.00 (122.00,124.70)	-3.728	< 0.001
CSF IgG	92.85 (55.48,149.25)	30.30 (20.90,40.60)	-10.443	< 0.001
Qalb ($\times 10^{-3}$)	9.41 (6.64,11.17)	4.96 (3.72,6.21)	-9.247	< 0.001
Data are presented as n (%) for categorical variables and median (P25, P75) for continuous variables with non-normal distributions. Between-group comparisons were performed using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Qalb, cerebrospinal fluid/serum albumin quotient; CSF, cerebrospinal fluid; WBC, white blood cell; IgG, immunoglobulin G; ALT, alanine aminotransferase. A two-sided P value < 0.05 was considered statistically significant.				

Laboratory characteristics

Among the serum parameters examined, serum glucose, total bilirubin, ALT, and creatinine differed significantly between the NS and NNS groups (all $P < 0.05$), whereas no significant between-group differences were observed in serum IgG or chloride levels. For CSF parameters, the proportion of patients with a positive Pandy's test was significantly higher in the NS group than in the NNS group [43 (50.00%) vs. 7 (3.60%), $P < 0.001$]. Patients with NS also had higher CSF albumin concentrations, WBC counts, chloride concentrations, IgG levels, and Qalb values than patients without NS (all $P < 0.001$). No statistically significant difference was observed in CSF glucose between groups ($P = 0.061$) (Table 1).

Multivariable analysis of factors associated with neurosyphilis

Variables showing statistically significant differences in univariable analyses were further evaluated using multivariable binary logistic regression. In multivariable binary logistic regression, age, serum glucose, CSF albumin, CSF WBC count, CSF IgG, Pandy's test, and Qalb were significantly associated with neurosyphilis, whereas serum creatinine was not statistically significant ($P = 0.126$) (Table 2).

Table 2
Multivariable logistic regression analysis of factors associated with neurosyphilis

Variables	β	SE	Wald χ^2	P value	Adjusted OR (95% CI)
Age	0.046	0.017	7.316	0.007	1.047 (1.013–1.082)
Serum glucose	0.534	0.220	5.923	0.015	1.706 (1.110–2.623)
Serum creatinine	0.015	0.010	2.340	0.126	1.015 (0.996–1.036)
CSF albumin	0.599	0.090	44.236	< 0.001	1.820 (1.525–2.171)
CSF WBC count	0.198	0.053	14.112	< 0.001	1.219 (1.099–1.351)
CSF IgG	0.025	0.007	13.309	< 0.001	1.025 (1.011–1.038)
Pandy's test	−3.645	0.553	43.437	< 0.001	0.026 (0.009–0.077)
Qalb	−0.509	0.072	17.080	< 0.001	0.601 (0.523–0.692)

β , regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; CSF, cerebrospinal fluid; WBC, white blood cell; IgG, immunoglobulin G; Qalb, CSF/serum albumin quotient. A two-sided P value < 0.05 was considered statistically significant.

Diagnostic performance of selected indicators

ROC curve analysis was performed to evaluate the discriminative performance of selected clinical and laboratory indicators for neurosyphilis. CSF IgG showed the highest discriminative performance, with an AUC of 0.902 (95% CI 0.856–0.948), followed by CSF albumin (AUC 0.871; 95% CI 0.818–0.924), Qalb (AUC 0.867; 95% CI 0.814–0.919), and CSF WBC count (AUC 0.815; 95% CI 0.750–0.880). Age showed moderate discrimination (AUC 0.701; 95% CI 0.633–0.768). Serum creatinine and serum glucose showed

lower discriminative performance, with AUCs of 0.666 (95% CI 0.594–0.737) and 0.631 (95% CI 0.553–0.708), respectively (Fig. 1).

The optimal cutoff value for CSF IgG, determined using the Youden index, was 54.7, yielding a sensitivity of 79.2% and a specificity of 91.0% for distinguishing patients with neurosyphilis from those without neurosyphilis.

Discussion

In this retrospective study of 281 patients with syphilis who underwent CSF examination, 86 were classified as having neurosyphilis. Patients with NS were older and more frequently male than patients with NNS, and several serum and CSF laboratory variables differed between groups. In multivariable analysis, age, serum glucose, CSF albumin, CSF WBC count, CSF IgG, Pandy's test, and Qalb were associated with NS. Among the individual indicators evaluated by ROC analysis, CSF IgG had the highest AUC.

Age differed substantially between the NS and NNS groups. Previous literature has also described demographic differences in contemporary syphilis and neurosyphilis populations [3]. Male patients were more common in the NS group in the present study; however, because sex was not included among the variables reported in the final multivariable model, this finding is best interpreted as a between-group association rather than as evidence of an independent effect.

Serum glucose levels were higher in patients with NS than in patients with NNS. Previous work has reported an association between elevated HbA1c and blood–brain barrier disruption in patients with syphilis [5]. The present study was retrospective and observational, so the finding should not be interpreted as establishing a causal relationship between glucose metabolism and neurosyphilis. Rather, it suggests that serum glucose may warrant consideration as part of the broader clinical assessment.

CSF abnormalities were more pronounced in patients with NS. Higher CSF albumin concentrations and WBC counts are consistent with altered barrier function and inflammatory changes in the central nervous system. CSF IgG concentrations were also markedly higher in the NS group. Intrathecal immunoglobulin synthesis has been described in neurosyphilis [4, 8], which may partly explain this finding. In the present ROC analysis, CSF IgG showed the highest AUC among the evaluated individual indicators. This supports its potential value as an adjunctive marker, but it should not be regarded as a stand-alone diagnostic test and should be interpreted together with serological findings, other CSF parameters, and the clinical context.

Qalb was significantly higher in the NS group than in the NNS group. The albumin quotient is commonly used as an indicator of blood–CSF barrier function and is not specific to neurosyphilis [10]. The observed difference may therefore reflect greater blood–CSF barrier dysfunction rather than a disease-specific process. Likewise, a positive Pandy's test was substantially more frequent among patients with NS, but this finding should be regarded as supportive rather than specific evidence.

Several limitations should be considered. First, the retrospective design may have introduced selection and information bias. Second, only patients with syphilis who underwent CSF examination were included, so the study population may not represent all patients with syphilis. Third, patients with confirmed HIV infection were excluded; therefore, the findings may not be generalizable to patients with HIV–syphilis coinfection. Fourth, some CSF abnormalities evaluated in the study also formed part of the diagnostic criteria for neurosyphilis, which may have increased the apparent discriminative performance of related CSF indicators. Fifth, the study was conducted at two affiliated hospitals in the same region and external validation in an independent population was not performed. Sixth, some laboratory variables contained missing observations and analyses were performed using available data. Finally, information on sexual orientation was not available. Larger prospective studies and external validation are needed to confirm the findings and determine the clinical utility of the identified indicators.

Conclusions

In this retrospective observational study of patients with syphilis undergoing CSF examination, neurosyphilis was associated with older age and several abnormalities in serum and CSF laboratory parameters. CSF IgG showed the highest discriminative performance among the evaluated individual indicators and may provide useful adjunctive information in the clinical assessment of neurosyphilis. These findings should be interpreted in conjunction with established diagnostic criteria and require validation in larger, independent populations.

Abbreviations

ALT	
alanine aminotransferase	
AUC	
area under the receiver operating characteristic curve	
CI	
confidence interval	
CSF	
cerebrospinal fluid	
HIV	
human immunodeficiency virus	
IgG	
immunoglobulin G	
NNS	
non–neurosyphilis	
NS	
neurosyphilis	
OR	
odds ratio	

Qalb
cerebrospinal fluid/serum albumin quotient
ROC
receiver operating characteristic
TPPA
Treponema pallidum particle agglutination assay
TRUST
toluidine red unheated serum test
WBC
white blood cell

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (approval no. YX2025–183) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. For participants younger than 18 years, written informed consent was obtained from their parents or legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

P.G. contributed to data collection, figure preparation, data analysis, and drafting of the original manuscript. X.J. contributed to manuscript editing and language polishing, data verification, and coordination of the manuscript submission. H.Z. contributed to manuscript editing. J.W. supervised the study, contributed to data collection, and served as the corresponding author. All authors reviewed and approved the final manuscript.

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Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

References

1. Wu S, Ye F, Wang Y, Li D. Neurosyphilis: insights into its pathogenesis, susceptibility, diagnosis, treatment, and prevention. *Front Neurol*. 2024;14:1340321. 10.3389/fneur.2023.1340321.
2. Cobanovic S, Kondziella D, Wille L, Haugbøl S. Ischaemic apoplexy caused by syphilis. *Ugeskr Laeger*. 2024;186(28). 10.61409/V01240040.
3. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med*. 2020;382(9):845–54. 10.1056/NEJMra1901593.
4. Alberto C, Lambeng N, Deffert C, Breville G, Gayet-Ageron A, Lalive P, et al. Multicentric evaluation of a specific intrathecal anti-*Treponema pallidum* IgG index as a diagnostic biomarker of neurosyphilis: results from a retro-prospective case-control study. *Sex Transm Infect*. 2024;100(2):63–9. 10.1136/sextrans-2023-055913.
5. Wang F, Ge H, Su X, Wang R, Zeng J, Miao J. High HbA1c level is correlated with blood-brain barrier disruption in syphilis patients. *Neurol Sci*. 2020;41(1):83–90. 10.1007/s10072-019-04031-x.
6. National Center for STD Control, Chinese Center for Disease Control and Prevention; Venereology Group, Chinese Society of Dermatology; Subcommittee on Venereology, China Dermatologist Association. Guidelines for diagnosis and treatment of syphilis, gonorrhea and genital Chlamydia trachomatis infection (2020). *Chin J Dermatol*. 2020;53(3):168–79. 10.35541/cjd.20190808.
7. Park IU, Tran A, Pereira L, Fakile Y. Sensitivity and specificity of treponemal-specific tests for the diagnosis of syphilis. *Clin Infect Dis*. 2020;71(Suppl 1)–S20. 10.1093/cid/ciaa349
8. Huang X, Ying S, Luo L, Li L, Li D, Xie Y. Intrathecal immunoglobulin synthesis and its role in patients with neurosyphilis. *Front Public Health*. 2022;10:1008595. 10.3389/fpubh.2022.1008595.

9. Gudowska–Sawczuk M, Mroczko B. Chemokine ligand 13 (CXCL13) in neuroborreliosis and neurosyphilis as selected spirochetal neurological diseases: a review of its diagnostic significance. *Int J Mol Sci.* 2020;21(8):2927. 10.3390/ijms21082927.
10. Castellazzi M, Morotti A, Tamborino C, Alessi F, Pilotto S, Baldi E, et al. Increased age and male sex are independently associated with higher frequency of blood–cerebrospinal fluid barrier dysfunction using the albumin quotient. *Fluids Barriers CNS.* 2020;17(1):14. 10.1186/s12987-020-0173-2.

Figures

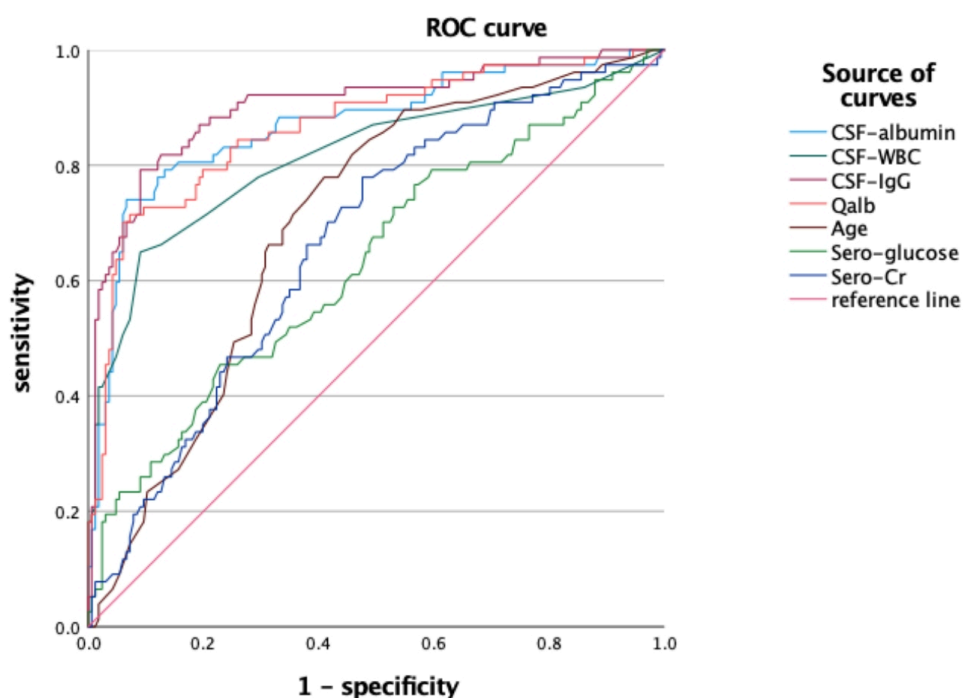


Figure 1

Receiver operating characteristic curves of selected indicators for neurosyphilis

Receiver operating characteristic curves for CSF albumin, CSF white blood cell count, CSF IgG, Qalb, age, serum glucose, and serum creatinine. The corresponding AUC values were 0.871, 0.815, 0.902, 0.867, 0.701, 0.631, and 0.666, respectively. AUC, area under the receiver operating characteristic curve; CSF, cerebrospinal fluid; IgG, immunoglobulin G; Qalb, cerebrospinal fluid/serum albumin quotient.

Supplementary Files

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