Inflammation may be correlated with Symptomatic Neurosyphilis

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Research article

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Abstract

Background A retrospective study was performed to compare the differences in clinical and laboratory features of asymptomatic neurosyphilis (ANS) and symptomatic neurosyphilis. Methods One hundred and four eligible patients were enrolled from the beijing ditan hospital between February 2017 and June 2018, including 35 ANS and 69 symptomatic neurosyphilis. The clinical data was analyzed retrospectively, including age, sex, treatment history, serum Alb, neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), CRP, RPR, rapid plasma reagin(RPR), as well as CSF RPR, CSF Alb, CSF WBCs, and CSF protein. Results Of the one hundred and four inpatients, there were significant differences in age, male, serum RPR, CSF protein, NLR, PLR, CSF-Alb /S-Alb and CRP between the two groups. The multivariate logistic regression analysis revealed that CSF protein (OR 1.07, 95%CI 1.024-1.118, P=0.002) , serum RPR (OR 1.035, 95%CI 1.001-1.059, P=0.003) and NLR (OR 2.568, 95% CI 1.226-5.376, P=0.012) were independent risk predictors for symptomatic neurosyphilis. Female (OR 0.11, 95% CI 0.025-0.490 , P=0.004) was protective factor for symptomatic neurosyphilis. Conclusions Male gender, serum RPR, CSF protein and NLR were risk factors for symptomatic neurosyphilis. They may indicate the development and aggravation of neurosyphilis Moreover, the ROC showed that NLR ≥ 3.348 could better predict the development of symptomatic neurosyphilis. Inflammation was significantly correlated with the development of neurosyphilis at discharge.

Background

Neurosyphilis is a chronic sexually transmitted disease of central nervous system (CNS) caused by Treponema pallidum [1-3]. According to the presentation of neurologic symptoms or signs, NS is categorized into asymptomatic NS (ANS) and symptomatic NS. ANS have serologic and clinical evidence, with cerebrospinal fluid (CSF) WBCs, elevated protein, positive CSF RPR[2]. But they have no neurological symptoms. The presentations of symptomatic NS include acute or chronic change in mental status, ataxia, weakness, numbness, cognitive decline and cranial nerve dysfunction,including meningeal, meningovascular, paralytic dementia, tabes dorsalis and gummatous[4].Symptomatic NS is very dangerous to human beings, and often remain irreversible neurological deficits, we should pay more attention to symptomatic NS. There is no study about the laboratory data features of symptomatic and asymptomatic NS in immunodeficiency virus (HIV) negative patients.

Recently, a number of studies have focused on determining the appropriate inflammatory factors to predict the outcome of patients with various neurological diseases. As clinically easily available inflammatory factors, the increased C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood have been confirmed to be correlated with poor outcome in AIS[5]. CRP is a blood biomarker produced by the liver representing acute-phase systemic inflammation. CRP can accurately detect low-grade inflammation and is widely used in clinical practice[6]. Recently, the NLR and platelet-to-lymphocyte ratio(PLR) became relatively reliable indicators of ongoing destructive inflammation [7-8]. Moreover, NLR was believed to be more stable and valuable than single changes in neutrophil or lymphocyte [9].

In this study, we retrospectively evaluated NLR, PLR, CSF albumin (Alb), serum-Alb, serum RPR, CRP, CSF WBCs ,CSF RPR and CSF protein, as well as sex, age, history of syphilis were investigated and explored the risk factors of symptomatic NS.

Methods

Patient recruitment

A total of one hundred and ninety five eligible patients with positive serum RPR underwent lumbar puncture (LP) to rule out neurosyphilis. Because the patients had neurological symptoms or a serofast status without clinical symptoms or signs in the neurology department of Beijing Ditan hospital, Capital Medical University, Beijing, China, between February 2017 and June 2018 . From these patients, one hundred and four patients(104/195, 53.33%) were diagnosed NS and enrolled in this study. The NS patients were all positive in serum RPR, with or without neurological symptoms. All of the cerebrospinal fluid (CSF) underwent testing with RPR, TPPA , white blood cells (WBCs) and protein level, as well as serum RPR, TPPA , and hemogram. Albumin levels in CSF and plasma were measured in 20 symptomatic NS patients and 20 ANS patients to assess blood-brain barrier (BBB) integrity and the albumin ratio (CSF/serum, QAlb). This cohort study was conducted the inclusion criterias include: (1) TPPA and RPR were positive in serum; (2) TPPA and RPR were positive in CSF; (3) HIV negative. The stage of syphilis was determined according to the Centers for Disease Control and Prevention guidelines[10]. Past studies have shown that the higher the QAlb, the more serious the BBB damage. When QAlb is > 10 $*10^{-3}$, there should be BBB damage, and > 30 $*10^{-3}$ (severe damage) , 10 ~30 $*10^{-3}$ (moderate damage), and 7.5~10 $*10^{-3}$ (mild damage)[11]. NS patients were divided into ANS group and symptomatic NS group according to the absence or presence of neurologic symptoms or signs. ANS was defined as syphilis of any stage that met the laboratory criteria for neurosyphilis but without clinical symptoms or signs. symptomatic NS was defined as syphilis of any stage that met the laboratory criteria for neurosyphilis with clinical symptoms or signs. This study was approved by the Ethics Committee and Institutional Review Board of Beijing Ditan Hospital, Capital Medical Univesity.

Data collection

Data of serum hemogram, Alb, C-reactive protein (CRP), serum and CSF TPPA and RPR, CSF WBCs, CSF Alb, as well as CSF protein were collected. As we know, CSF venereal disease research laboratory (VDRL) test is the reference test for the laboratory diagnosis of NS. However, there are no commercial VDRL reagents approved by the State Food and Drug Administration for VDRL examination in China. There are research suggesting that RPR can be considered as an alternative test for NS diagnosis when the VDRL is not available[12]. In this study, CSF RPR is used to diagnose NS, given that the specificity and sensitivity of RPR are similar to VDRL and rapid plasma reagin (RPR), but they are easier and less expensive to perform[13].

Statistical analysis

All data were analyzed using the IBM SPSS Statistics version 17. Continuous data following Gaussian distribution were displayed as mean±standard deviation(SD), and were analyzed using the independent samples T test. Otherwise, they were presented as a median with interquartile range (IQR) and analysed with Mann-Whitney U test or variance analysis. Meanwhile, $\chi 2$ for categorical variables. The independent variables associated with the symptomatic NS were analyzed by logistic regression analysis. Possible confounding factors were tested in a univariable regression analysis. Factors with a P value < 0.1 were tested in a multivariable logistic regression analysis. The receiver operating characteristic (ROC) curve was used to demonstrate the sensitivity and specificity of significant variables and the optimal cutoff values for predicting the symptomatic NS. A difference between the groups was considered significant if $P < 0.05$.

Results

Demography data of patients

Of the 104 NS patients, 66.35%(69/104) were symptomatic NS and 33.65% (35/104) were ANS. They had high risk sexual behavior or were infected by their sex partners. In the symptomatic NS group, the age ranged 20~72 years, and the average age was 50 years. 2 cases received benzathine penicillin G treatment prior to the diagnosis of neurosyphilis. The history of syphilis infection ranged 5~40 years, and the average time was 18 years. In the ANS group, the age ranged 24~66 years, and the average age was 40 years. 33 cases received benzathine penicillin G treatment. The history of syphilis infection ranged 2~10 years, and the average time was 5 years. There were significant differences in age and sex between the two groups (all p<0,001, Table 1).

laboratory data

There were significant differences in serum RPR , CSF protein, NLR, PLR and CRP between the two groups (Table1). The QAlb values of symptomatic NS group differed significantly from those of ANS group [$(23.11\pm9.27)*10^{-3}$ vs $(11.7\pm2.39)*10^{-3}$, P=0.046). Logistic regression was used to study the value of biomarkers in predicting the symptomatic NS. The independent variables were the baseline levels of serum RPR , CSF protein, NLR, PLR and CRP . The multivariate logistics analysis found that the baseline CSF protein, serum RPR and NLR were significantly associated with high risk of symptomatic NS (adjusted OR1.07, 95%CI 1.024-1.118, P=0.002; adjusted OR 1.035, 95%CI 1.001-1.059, P=0.003; adjusted OR 2.568, 95% CI 1.226-5.376, P=0.012) . Female (adjusted OR 0.11, 95% CI 0.025-0.490, P=0.004) was protective factor for symptomatic neurosyphilis (Table2).

The ROC curve demonstrated the predicting power of baseline serum NLR on the symptomatic NS with an area under the curve value of 0.783 (P< 0.001, 95% CI 0.69–0.876, the sensitivity was 71%, and the specificity was 80%) (Fig. 1). The optimal cutoff is 3.348. To further estimate the significance of baseline NLR on predicting the the symptomatic NS, NS patients were divided into two groups according to the

cutoff value of NLR (NLR < 3.348 and≥3.348). The results revealed that the group with NLR ≥ 3.348 had higher incidence of symptomatic NS than that of asymptomatic NS(88.87% vs 42%, P < 0.001).

Discussion

In recent years, the prevalence of syphilis is increasing, and about 10% to 25% of untreated syphilis will develop to NS, and 23% ~87% untreated ANS will develop to symptomatic NS[2]. The involvement of CNS may cause functional impairment at early stage or irreversible organic dysfunction at late stage, or even death. Hence, clinicians should pay much attention to the related risk factors. Several previous studies concerned with risk factors of neurosyphilis in syphilis found that neurosyphilis was more prevalent in male and higher serum RPR[14]. Li et al found that symptomatic NS was more prevalent in male gender, age≥45 years, lack of antisyphilis treatment, higher serum RPR, CSF protein concentration, and CSF RPR titer[15]. In our study, we took several inflammatory factors into consideration and to explore the role of inflammation in symptomatic NS.

In our study, there were more males in the symptomatic NS group (54/69, 78.26%) than in the ANS group (14/35, 40%). The result was consistent with previous studies[16].

As we know, NS is a chronic inflammation of CNS. Hence, the BBB damage and inflammation play an important role in the development of diseases. Abnormal CSF protein may be associated with the development of NS, while abnormal CSF WBCs may play a continuing role in the NS progression. In this study, the differences of CSF WBCs in ANS and symptomatic NS patients have no statistical significance, indicating that the CSF WBCs is indifferent. It is often possible to be along with the whole process of NS. When the BBB is damaged, the CSF protein increases. Increased CSF protein may represent the severity of the brain damage[17]. In the study, the concentrations of CSF protein in the symptomatic NS group was higher than that in the ANS group. Further study inferred that high CSF protein concentration was an independent risk factor for symptomatic NS (OR=1.07, P=0.002). Hence, if the CSF protein concentration increases, it may indicate the progress of the disease, and timely treatment is necessary. As we know, reduction of CSF drainage from the cranio-spinal space, inflammation induced-protein production as well as BBB damage have been suggested as possible causes of increased concentration of CSF proteins[18].Our study showed that the QAlb in the symptomatic NS group was significantly higher than in the ANS group, suggesting that the BBB damage was more severe in the symptomatic NS group. This may explain why the symptomatic NS group had higher CSF protein. We speculated that higher CSF protein may be related to the BBB damage. However, our data could not prove whether CSF protein was increased by CNS infection, and further studies are needed to evaluate the reasons.

Recently, hemogram is the most commonly, rapidly and widely available laboratory method, hence, it has been reported that NLR and PLR represent a novel composite inflammatory marker. They have been proven to correlate with CRP, as well as they have a prognostic value among patients with cancer, coronary artery disease, and some CNS diseases, such as traumatic brain injury, intracranial hemorrhage, and cerebral venous thorombosis[19-23], However, to be best of our knowledge, there was no study

between NS and NLR. As clinically easily available biomarkers, CRP and NLR in the peripheral blood were used in our study to represent the inflammatory response. According to our results, the differences of CSF WBCs in ANS and symptomatic NS patients have no statistical significance. We speculated the reason may be NS was a chronic inflammatory, and CRP was a biomarker of acute inflammation. The study reavealed that the levels of serum NLR was higher in symptomatic NS patients compared with those in ANS patients (OR=2.568, P=0.012). It indicated that inflammation may play an important role during the course of NS. In other words, the degree of inflammation may indicate the progress of the disease. Different levels of NLR might present clinical types of NS. Furthermore, The ROC curve showed that an NLR≥3.348 could better predict the development of symptomatic neurosyphilis, suggesting that baseline inflammation could influence and predict the symptomatic NS. Hence, it is suggested that a significant correlation between inflammation and symptomatic NS and inflammatory activity was more obvious in symptomatic NS patients. An chronic inflammatory process maybe initiated by the treponema pallidum and it can result in CNS damage[24].

There are some limitations in this study. First, this was just a single-center study. Second, the number of cases enrolled was small, which may result in the selection bias. Third, this study did not explore the mechanisms what substances mediate NLR changes after symptomatic NS. Further studies with multi-centers and large number of cases are still needed, and explore the difference biomarkers between different types of symptomatic NS.

Conclusions

Male gender is a risk factors for symptomatic NS. Serum RPR, CSF protein concentration and NLR may indicate the development of neurosyphilis and the aggravation of neurological symptoms. Our results support the role of inflammatory theory in the pathogenesis of symptomatic NS and changes with the course of NS.

Abbreviations

CNS central nervous system

NS neurosyphilis

ANS asymptomatic NS

CSF Cerebrospinal fluid

RPR toluidine red untreated serum test

TPPA Treponema pallidum particle assay

VDRL venereal disease research laboratory

RPR rapid plasma reagin

HIV human immunodeficiency virus

NLR neutrophil to lymphocyte ratio

PLR platelet-to-lymphocyte ratio

CRP C-reactive protein

WBCs white blood cells

IQR interquartile range

BBB blood-brain barrier

LP lumbar puncture

Declarations

Ethical Approval and Consent to participate

This study was approved by the Institutional Review Board of Beijing Ditan Hospital (2018-044-01). All patients provided written informed consent before enrolment.

Consent for publication

The authors and all patients agree to publish, including any individual person’s data in any form (including individual details, images).

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WY coordinated the study, collected and analyzed the data, and drafted the manuscript. HY and XD collected data and helped to modify the manuscript. WW was corresponding author and participated in

its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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ICMJE Statement

All authors meet the ICMJE authorship criteria.

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Tables

Table 1 The Demography and laboratory data of NS patients(n=104)

Due to technical limitations, Table 1 is only available as a download in the supplemental files section.

Table 2 The logistic regression analysis for clinical and laboratory predictors of symptomatic NS patients

factor	β	OR	95%CI	P Value
Sex(female vs male)	-2.211	0.11	0.025~0.490	0.004
Serum RPR	0.034	1.035	1.011~1.059	0.003
CSF Protein	0.068	1.07	1.024~1.118	0.002
NLR	0.948	2.568	1.226~5.376	0.012
CRP	-.087	0.917	0.714~1.178	0.494
PLR	-.004	0.996	0.98~1.007	0.494

Figures

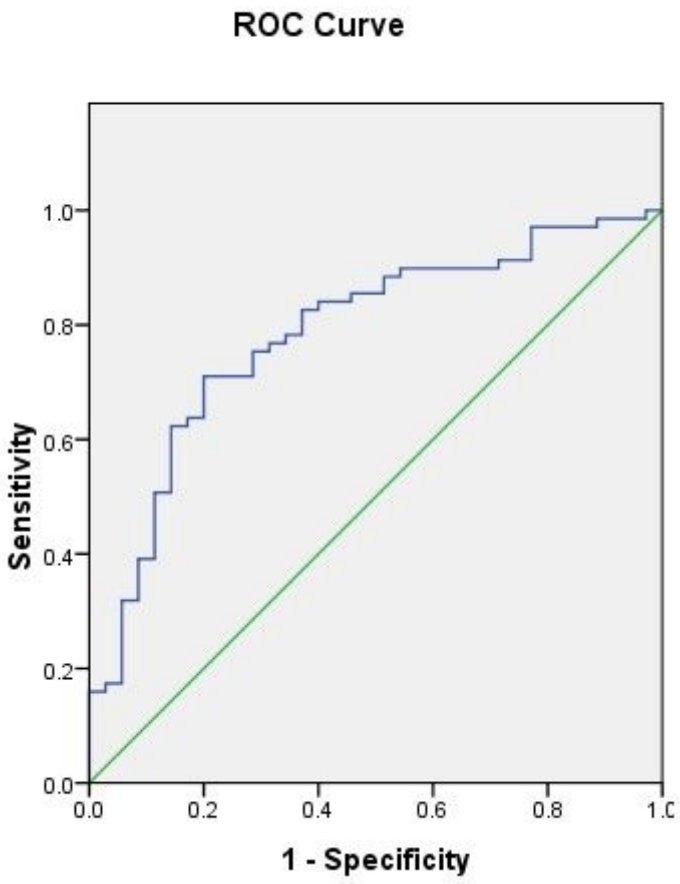

Figure 1

Receiver operating characteristic (ROC) curve for serum NLR on predicting symptomatic NS(AUC0.783, 95% CI 0.69–0.876, P< 0.001).

Supplementary Files

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- supplement1.jpg