Comparison of Laboratory Features of Symptomatic and Asymptomatic Neurosyphilis

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Research article

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Abstract

Background Neurosyphilis is a chronic sexually transmitted disease involving central nervous system caused by *Treponema pallidum* and can affect any part at any stage of infection. Neurosyphilis was categorized as asymptomatic neurosyphilis and symptomatic neurosyphilis, and symptomatic neurosyphilis is very dangerous to human beings and can cause organic damage. However, its characteristics are not very clear. In this paper, we want to compare the laboratory characteristics of the asymptomatic neurosyphilis and symptomatic neurosyphilis. **Methods** A total of 118 eligible patients in Beijing Ditan Hospital were enrolled in this retrospectively registered study between February 2017 and June 2018. The clinical data were analyzed retrospectively, including age, sex, standardized treatment, serum Alb, neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), CRP, TRUST, as well as CSF TRUST, Alb, CSF WBCs, and CSF protein before treatment. **Results** Of the 118 patients, there were significant differences in age, serum TRUST, CSF TRUST, CSF protein, NLR, PLR, CSF-Alb/S-Alb and CRP between the two groups. According to multivariate regression analysis, CSF protein (OR 1.051, 95% CI 1.015-1.088, $P=0.005$) and NLR (OR 2.461, 95% CI 1.321-4.584, $P=0.005$) were significantly associated to symptomatic neurosyphilis. **Conclusions** NLR and CSF protein levels should be taken into account as potential biomarkers of symptomatic neurosyphilis, especially NLR, as it is inexpensive parameters, noninvasive, and widely available, it can be used in clinical practice for prediction of symptomatic neurosyphilis.

Background

Syphilis is a chronic sexually transmitted disease caused by *Treponema pallidum*. Central nervous system invasion of syphilis is called neurosyphilis (NS) and can occur any part at any stage[1-3]. According to the presentation of neurologic symptoms or signs, NS was categorized as asymptomatic NS (ANS) and symptomatic NS, and the latter involved meningeal, meningovascular, paralytic dementia, tabes dorsalis and gummatous[4]. The presentation of symptomatic NS included acute or chronic change in mental status, ataxia, weakness, numbness, cognitive decline and cranial nerve dysfunction. Because symptomatic NS is very dangerous to human beings, and often remained irreversible neurological deficits, we should pay more attention to symptomatic NS. Because there was no study about the laboratory data features of symptomatic and asymptomatic NS in immunodeficiency virus (HIV) negative patients. In this article, We designed a single-center retrospective cohort study, data were collected from Beijing Ditan hospital between between February 2017 and June 2018 and to evaluate the potential predictive value of neutrophil to lymphocyte ratio (NLR) in NS patients. In addition, other available laboratory parameters, including platelet-to-lymphocyte ratio (PLR) and other biomarkers, such as CSF Albumin (Alb), Serum-Alb, TRUST, CRP, CSF WBCs and CSF protein as well as sex, age, history of syphilis were investigated.

Methods

Patient recruitment

A total of 111 eligible patients with NS in the neurology department of Beijing Ditan hospital, Capital Medical University, Beijing, China, between February 2017 and June 2018 were enrolled in this study after they signed the content form. The NS patients were all positive for serum tolulized red unheated serum test (TRUST), with neurological symptoms or regular treatment with penicillin after more than 2 years, but the serum TRUST did not decrease or increase, hence lumbar puncture (LP) was performed in all the 111 patients. All of the cerebrospinal fluid (CSF) underwent testing with TRUST, TPPA, white blood cells (WBCs) and protein level, as well as serum TRUST, 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 TRUST were positive in serum; (2) TPPA and TRUST were positive in CSF; CSF TRUST was negative, but WBCs $\geq 5/\mu\text{L}$ or CSF protein $\geq 45\text{mg/dL}$, and there was no evidence of other central nervous system (CNS) diseases which can cause elevated CSF WBCs or protein[5]; (3) HIV negative. The stage of syphilis was determined according to the Centers for Disease Control and Prevention guidelines[6]. Past studies have shown that the higher the QAlb, the more serious the BBB damage. When QAlb is $> 10 \times 10^{-3}$, there should be BBB damage, and $> 30 \times 10^{-3}$ (severe damage), $10 \sim 30 \times 10^{-3}$ (moderate damage), and $7.5 \sim 10 \times 10^{-3}$ (mild damage)[7]. NS patients were divided into ANS group and symptomatic NS group according to the absence or presence of neurologic symptoms or signs, such as cognitive impairment, limb weakness, numbness, headache, decreased vision, ataxia, and personality change. All NS patients received intravenous aqueous crystalline penicillin G, 4 million units intravenously every 4 hours for 14 days, followed by intramuscular injection of benzathine penicillin once a week at a dose of 2.4 million units for 3 consecutive sessions. This study was approved by the Ethics Committee and Institutional Review Board of Beijing Ditan Hospital, Capital Medical Univesity. All patients provided written informed consent before enrolment.

Data collection

Data of serum hemogram, Alb, C-reactive protein (CRP), serum and CSF TPPA and TRUST, 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 TRUST can be considered as an alternative test for NS diagnosis when the VDRL is not available [8]. In this study, CSF TRUST is used to diagnose NS, given that the specificity and sensitivity of TRUST are similar to VDRL and rapid plasma reagin (RPR), but they are easier and less expensive to perform[9].

Statistical analysis

All data were analyzed using the IBM SPSS Statistics version 17. Continuous data following Gaussian distribution were displayed as mean $\pm$ 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, χ^2 for categorical variables. The independent

influencing factors of NS used Logistic regression. A two-tailed $p < 0.05$ was considered statistically significant.

Discussion

Demography data of patients

Of the 111 NS patients, 62.16% (69/111) were symptomatic NS and 37.84% (42/111) were ANS. The transmission is unclean sexual behavior or the spouse is infected with syphilis. In the symptomatic NS group, The age ranged 20~72 years, and the average age is 50 years. 2 of whom had benzathine penicillin treatment before inpatient, and 67 had received no treatment. The history of syphilis infection ranged 5~40 years, and the average age is 18 years. In the ANS group, The age ranged 24~66 years, and the average age is 40 years. 40 of whom had benzathine penicillin treatment before inpatient, and 2 had received no treatment. The history of syphilis infection ranged 2~10 years, and the average age is 5 years. The dominant symptomatic NS was paralytic dementia. There were 65.22% (45/69) of paralytic dementia, 34.49 % (10/69) of tabes dorsalis, 4.35% (3/69) of meningeal, 13.04% (9/69) of meningovascular, and 2.9 % (2/69) of gummatous (Table 1).

Laboratory data

There were significant differences in serum TRUST, CSF TRUST , CSF protein, NLR, PLR and CRP between the two groups ($p < 0.05$, Table 2). The QAlb values of symptomatic NS group differed significantly from those of ANS group (23.11 ± 9.27 VS 11.7 ± 2.39 , $P=0.046$). With symptomatic dependent variables, biomarkers which had statistical differences in single factor analysis were carried out with logistic regression analysis. The result revealed that CSF protein (odds ratio (OR) 1.06, 95% CI 1.02~1.101, $P=0.003$) and NLR (OR 2.299, 95% CI 1.225~4.315, $P=0.01$) were independent influencing factors (Table 3).

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. However, the laboratory characteristics between ANS and symptomatic NS are not yet presently defined. In this study, we aimed to analysis the laboratory data between the two groups and find some differences.

Our results suggested that the history of symptomatic NS was longer than that of ANS, and the proportion of patients with symptomatic NS who had not been treated with penicillin before diagnosing syphilis was higher. There was a statistical difference between the two groups. The results also suggested that syphilis patients should be given standardized treatment as soon as possible in order to reduce the incidence of neurosyphilis, especially symptomatic neurosyphilis.

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 levels of CSF proteins and serum NLR were higher in patients with symptomatic NS compared with those in ANS. It indicated that inflammation may play an important role during the course. In other words, the degree of inflammation may change with the kind of the disease.

As we know, NS is a chronic inflammation of CNS. Therefore, 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[10]. In this study, the concentrations of CSF protein in the symptomatic NS group was higher than that in the ANS group. 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[11]. 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 has higher CSF protein, and we speculated that higher CSF protein may be related to BBB damage. However, our data can only not prove whether CSF protein was increased by CNS infection induced their own production, and further studies are needed to evaluate the reasons.

Recently, Because of serum hemogram is cheap and easy, and it is the most commonly, rapidly and widely available laboratory method, hence, it has been reported that NLR and PLR represents a novel composite inflammatory marker, and 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 thrombosis [12-18], However, to be best of our knowledge, there was no study between NS and NLR. In this study, we analyzed the NLR in 111 NS patients and found that different clinical types of NS might present with different levels of NLR. NLR in the symptomatic NS group was higher than the ANS group. Hence, it is suggested that a significant correlation between inflammation and symptomatic NS may exist. An inflammatory process maybe initiated by the treponema pallidum and it can result in CNS damage. This also suggested the importance of early syphilis treatment.

There are some limitations in this study: First, this was just a single-center study. Second, the number of cases enrolled is 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

Syphilis patients should be given standardized treatment as soon as possible in order to reduce the incidence of neurosyphilis, especially symptomatic neurosyphilis. Meanwhile, we found that an increased CSF protein and NLR were shown to be independent predictors for symptomatic NS. The higher the CSF protein and NLR, the greater the possibility of symptomatic NS. Our result supports the role of inflammatory theory in the pathogenesis of symptomatic NS. Therefore, NLR and CSF protein may have a significant correlation with NS classification.

Abbreviations

CNS central nervous system

NS neurosyphilis

ANS asymptomatic NS

CSF Cerebrospinal fluid

TRUST 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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Tables

Table 1 The Demography data of NS patients

	ANS(n, %)	Symptomatic NS
Cases(n, %)	42(37.84%)	69(62.16%)
Male(n,%)	17(40.48%)	54(78.26%)
age(y)	40.12 ±9.83	49.77 ±10.40
Paralytic dementia		45(65.22%) 10(34.49%)
Tabes dosalis		3(4.35%)
Meningeal meningovascular		9(13.04%)
gummatous		2(2.9%)

Table 2 The laboratory data of symptomatic NS and ANS

	ANS	Symptomatic NS	P Value
Serum TRUST(median)	12□8~32□	32□8~64□	0.00
CSF TRUST(median)	0□0~1□	2(□1~4)	0.00
CSF WBC(median)	10□7~18□	15□7~40□	0.146
CSF Protein(mean ± SD)	37.27 ±14.61	67.13 ±33.20	0.00
NLR(mean ± SD)	2.64 ±1.07	4.27□3.15~5.27□	0.00
PLR(median)	118.49□93.31~180.26□	185.05 ±68.85	0.00
CRP(median)	0.5□0.3~1.03□	1.3□0.53~3.48□	0.00
QAlb(mean ± SD)	11.7±2.39	23.11±9.27	0.046

Table 3 The logistic regression analysis

factor	β	OR	95%CI	P value
CSF TRUST	0.406	1.5	0.926~2.43	0.02
CSF Protein	0.058	1.06	1.02~1.101	0.003
NLR	0.833	2.299	1.225~4.315	0.01
CRP	0.143	1.154	0.893~1.491	0.274
PLR	-.007	0.993	0.98~1.007	0.337
serum TRUST	0.02	1.021	1~1.042	0.052