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Research article

Clinical and laboratory features of neurosyphilis: A single-center, retrospective study of 402 patients

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ABSTRACT

Neurosyphilis is a serious global health issue and a big challenge in developing countries, related risk factors should be taken seriously. Although there are a certain number of studies describing the clinical and laboratory features and risk factors for symptomatic neurosyphilis (SNS), but some risk factors are still controversial. The aim of this research is to investigate the association between asymptomatic neurosyphilis (ANS) and symptomatic neurosyphilis (SNS) and identify risk factors for SNS. This was a single-center retrospective study in a tertiary hospital in Hangzhou, China. The clinical and laboratory features of neurosyphilis patients from January 1, 2011 to July 31, 2020 were retrospectively reviewed. After detailed assessments based on diagnostic criteria, 402 patients with neurosyphilis were enrolled in this study. There were 299 male and 103 female patients. The median age was 53.5 (45, 61) years. Multivariable logistic regression displayed that SNS were correlated with the following factors: male, without anti-syphilis treatment, high pretreatment serum RPR titer and positive CSF RPR. Our findings suggest a potential association between SNS and specific factors, including male gender, elevated pretreatment serum and CSF RPR titers. Moreover, our observations indicate that individuals without anti-syphilis treatment may be at a higher likelihood of manifesting the symptomatic form. This underscores the importance of considering gender, RPR titers, and treatment status as significant contributors to the risk profile for SNS.

1. Introduction

Neurosyphilis is the infection of central nervous system by *Treponema pallidum*, which caused syphilis reported expanding in China and worldwide [1,2]. In China, 438,199 newly cases of syphilis were reported in 2016, with an average annual increase of 8.6% from 2007 to 2016 [2]. Since 2000, the United States has witnessed a yearly rise in cases of primary and secondary syphilis, reaching a rate of 9.5 cases per 100,000 persons in 2017 [1]. About 3.5% of the patients with clinical manifestations of syphilis were diagnosed neurosyphilis on the basis of cerebrospinal fluid (CSF) results [3]. Neurosyphilis is generally categorized as asymptomatic neurosyphilis (ANS) and symptomatic neurosyphilis (SNS). ANS occurs in early infection of nervous system. Although ANS patients have positive laboratory test or clinical evidence of syphilis, but demonstrate no neurological symptoms [4]. ANS occurred in about 13.5%

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of latent syphilis patients, who were more likely to develop late neurological complications [5]. SNS would happen if ANS patients have persistent infection or do not been treated timely. SNS mainly include symptomatic syphilitic meningitis, meningovascular syphilis, general paresis, and tabes dorsalis [1]. Treatment of neurosyphilis could halt disease progression, while the stroke symptoms and signs may still arise. There are few data about the relationship between ANS and SNS. In our present study, we retrospectively analyzed the clinical and laboratory characteristics of 249 cases with SNS and 153 cases with ANS and explored the risk factors of SNS, which may be helpful in making clinical decisions.

2. Materials and methods

2.1. Study design and data collection

We reviewed the electronic medical records of neurosyphilis patients between January 2011 and July 2020 at the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China. After detailed assessments based on diagnostic criteria, 402 patients with neurosyphilis were enrolled in this study. All of these patients were HIV negative. Fig. 1 demonstrated the case screening process. This study was waived the need of informed consent by the ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (#2021-0447).

2.2. Diagnostic criteria

In this study, the diagnosis of neurosyphilis relied on the utilization of CSF-RPR and CSF-TPPA tests, in accordance with the diagnostic guidelines established by both the Centers for Disease Control (CDC) in America and Europe [6,7]. Confirmed neurosyphilis was designated for patients with positive CSF-RPR results. For cases where CSF-RPR was negative, presumptive neurosyphilis was considered if both of the following criteria were met: (a) positive CSF-TPPA, and (b) elevated CSF white blood cell (WBC) counts (>5/μL) or CSF protein concentration (>45 mg/dL), with no other identifiable causes for these abnormalities.

The patients were subdivided into ANS group and SNS group according to the clinical findings. ANS was defined as neurosyphilis but without clinical symptoms, while SNS was defined as neurosyphilis with symptomatic syphilitic meningitis, meningovascular syphilis, general paresis and tabes dorsalis, but without any other known causes for the clinical signs.

2.3. Statistical analysis

For variables with continuous data, the normal distribution was described as mean ± standard deviation, and the skewed

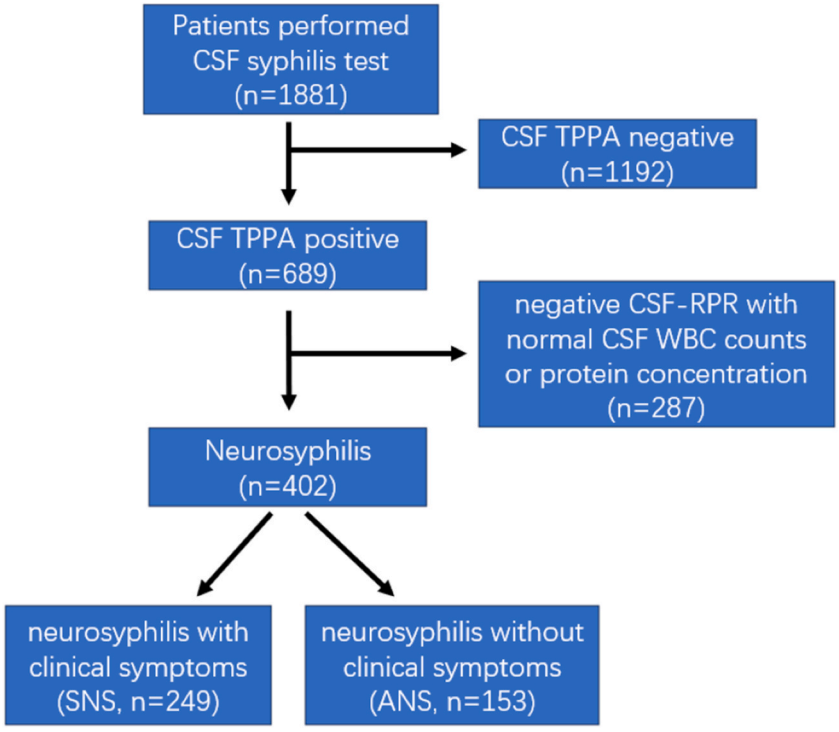

Fig. 1. "The flowchart of case screening process."

distribution was described as median (M) and quartile range (P_{25}, P_{75}). The categorical variables were described by numbers and percentages (%). The independent two-sample *t*-test was used to compare continuous variables and the chi-square test was used to assess the associations between categorical variables. Significant variables of univariate analysis ($P < 0.05$) were further identified in multivariate logistic regression analysis. $P < 0.05$ were considered to be statistically significant. All data analysis were conducted in SPSS 25.0 version.

3. Results

3.1. Patient demographics and clinical characteristics

This study has enrolled 402 neurosyphilis cases. The baseline features are shown in Table 1. There were 299 male and 103 female patients. The median age was 53.5 (45, 61) years.

153 (38.1%) patients were diagnosed as ANS, including 100 males and 53 females. The median age was 52 (42, 61) years. Among these patients, 67 cases had benzathine penicillin G treatment before their diagnosis of neurosyphilis, while the other 86 cases received no treatment. Prior to anti-neurosyphilis treatment, 136 patients had available baseline serum RPR titer (median titer, 1:8; IQR, 1:4, 1:32). There were 66 patients who had positive CSF RPR. 20 had RPR 1:1, 28 had RPR 1:2, 13 had RPR 1:4, 1 had RPR 1:8, 2 had RPR 1:16, 1 had RPR 1:32, and 1 had RPR 1:64. 69.4% of the patients (n = 93) had CSF WBC>5/μL, the median of which was 8 (4, 26)/μL. 80.4% of the patients (n = 111) had CSF protein concentration>45 mg/dL, the median of which was 54.8 (47.3, 74.9) mg/dL. All patients had positive TPPA in serum and CSF.

A total of 249 (61.9%) patients were diagnosed as SNS, the mean age of which was 53.62 ± 10.06 years. 199 males and 50 females were included. Among these patients, only 33 cases received benzathine penicillin G treatment prior to their diagnosis of neurosyphilis. Before anti-syphilis treatment, 238 patients had available baseline serum RPR titer (median titer, 1:32; IQR, 1:16, 1:64). 214 patients had positive CSF RPR titer, among which 31 had RPR 1:1, 50 had RPR 1:2, 60 had RPR 1:4, 44 had RPR 1:8, 17 had RPR 1:16, and 4 had RPR 1:32. 82.7% of the patients (n = 167) had CSF WBC>5/μL, the median of which was 20 (8, 52.5)/μL. 87.7% of the patients (n = 179) had CSF protein concentration>45 mg/dL, the median of which was 68.6 (54.4, 90.4) mg/dL. All patients had positive TPPA in serum and CSF.

Table 1
Demographics and baseline characteristics of the patients (N = 402).

Characteristics	SNS (249)	ANS (153)	*P* value
1. Sex (male: female)	199:50	100:53	$P = 0.001$
2. Age(years), mean ± SD/median year(IQR)	53.62 ± 10.06	52 (42, 61)	$P = 0.079$
≤30	3, 1.2%	14, 9.2%	NA
31∼40	22, 8.8%	19, 12.4%	NA
41∼50	67, 26.9%	33, 21.6%	NA
51∼60	93, 37.3%	47, 30.7%	NA
≥61	64, 25.7%	40, 26.1%	NA
3. Treatment history (yes: no)	33:216	67:86	$P < 0.001$
4. Pretreatment serum RPR titer, median (IQR)	1:32 (1:16, 1:64)	1:8 (1:4, 1:32)	$P < 0.001$
Negative (n, %)	37, 14.9%	11, 7.2%	NA
1:1(n, %)	0, 0%	0, 0%	NA
1:2(n, %)	7, 2.8%	15, 9.8%	NA
1:4(n, %)	17, 6.8%	29, 19.0%	NA
1:8(n, %)	24, 9.6%	22, 14.4%	NA
1:16(n, %)	39, 15.7%	25, 16.3%	NA
1:32(n, %)	55, 22.1%	20, 13.1%	NA
1:64(n, %)	41, 16.5%	11, 7.2%	NA
1:128(n, %)	12, 4.8%	2, 1.3%	NA
≥1:256(n, %)	6, 2.4%	1, 0.7%	NA
Not available (n, %)	11, 4.4%	17, 11.1%	NA
5. CSF RPR titer (positive: negative)	214:35	66:87	$P < 0.001$
1:1	31, 12.4%	20, 13.1%	NA
1:2	50, 20.1%	28, 18.3%	NA
1:4	68, 27.3%	13, 8.5%	NA
1:8	44, 17.7%	1, 0.7%	NA
1:16	17, 6.8%	2, 1.3%	NA
1:32	4, 1.6%	1, 0.7%	NA
1:64	0, 0%	1, 0.7%	NA
6. CSF WBC count, median (IQR),/μL	20 (8, 52.5)	8 (4,26)	$P < 0.001$
>5/μL (n, %)	167, 82.7%	93, 69.4%	$P = 0.004$
7. CSF protein concentration, median (IQR), mg/dL	68.6 (54.4, 90.4)	54.8 (47.3, 74.9)	$P < 0.001$
>45 mg/μL (n, %)	179, 87.7%	111, 80.4%	$P = 0.065$
8. CSF TPPA positive (n, %)	249, 100%	153, 100%	NA

Abbreviations: ANS = asymptomatic neurosyphilis; SNS = symptomatic neurosyphilis; RPR = rapid plasma regain; TPPA = *Treponema pallidum* particle agglutination; CSF = cerebrospinal fluid; WBC = white blood cells; NA = not available.

3.2. Comparison of clinical and laboratory results between SNS and ANS group

Through comparing the clinical characters between SNS and ANS group, we found that the SNS group had a significantly higher proportion of males (79.9%, 199/249) than in the ANS group (65.4%, 100/153) ($P = 0.001$). There was no significantly difference in the age between SNS group (mean age, 53.62 ± 10.06 years) and ANS group (median age, 52 years; IQR, 42–61 years) ($P = 0.079$). Additionally, the proportion of patients without anti-syphilis treatment in SNS group (86.7%, 216/249) were significantly higher than ANS group (56.2%, 86/153) ($P < 0.001$) (Table 1).

For the laboratory results, the pretreatment serum RPR titer in SNS group were significantly higher than in ANS group ($P < 0.001$). CSF results for syphilis demonstrated that the incidence of positive RPR titer was significantly higher in the SNS group (85.9%, 214/249) than in the ANS group (43.1%, 66/153) ($P < 0.001$). CSF WBC count (20/μL vs 8/μL), CSF WBC abnormal rate (82.7% vs 69.4%) and CSF protein concentration (68.6 mg/dL vs 54.8 mg/dL) were significantly higher in SNS group than ANS group ($P < 0.001$, $P = 0.004$ and $P < 0.001$, respectively), while there was no difference of CSF protein concentration abnormal rate (87.7% vs 80.4%) between the two groups ($P = 0.065$) (Table 1).

3.3. Logistic regression analysis

The bivariate analysis indicated that certain factors were associated with SNS, including being male (OR = 2.109, $P = 0.001$), aged 45 years or older (OR = 2.003, $P = 0.004$), absence of anti-syphilis treatment (OR = 0.196, $P < 0.001$), high pretreatment serum RPR titer (OR = 1.014, $P = 0.001$), positive CSF RPR (OR = 8.060, $P < 0.001$), and elevated CSF WBC count (OR = 2.104, $P = 0.005$) (Table 2). However, upon conducting multivariable logistic regression, it was found that SNS remained significantly associated with being male (OR = 2.187, $P = 0.009$), absence of anti-syphilis treatment (OR = 0.292, $P < 0.001$), high pretreatment serum RPR titer (OR = 1.014, $P = 0.007$), and positive CSF RPR (OR = 5.889, $P < 0.001$) (Table 2).

4. Discussion

Neurosyphilis is now a serious global health issue and still a big challenge in developing countries with a growing number of new cases [8,9]. ANS patients are likely to develop subsequent SNS. About 35% of the ANS patients would progress to SNS [4]. Therefore, related risk factors should be taken seriously. Earlier research has identified various risk factors associated with neurosyphilis, such as being male, aged 45 years or older, lack of anti-syphilis therapy, elevated serum RPR titers, positive CSF RPR, and high CSF protein concentration in HIV-negative individuals [4,10–12]. To furtherly assess whether these risk factors were also associated with SNS, we employed all these factors in our study.

Firstly, positive CSF RPR was considered to be correlated with neurosyphilis [13,14]. Our study revealed more positive CSF RPR patients in SNS group (214/249, 85.9%) than ANS group (66/153, 43.1%) ($P < 0.001$) (Table 1), which was supported by the univariate analysis result (OR = 8.060 $P < 0.001$) (Table 2). Further multivariate analysis displayed that positive CSF RPR was an independent risk factor for SNS (OR = 5.889, $P < 0.001$), which is consistent with previous report [4].

Secondly, univariate analysis shown that there were more males in SNS patients (199/249, 79.9%) than in ANS patients (100/153, 65.4%) (OR = 2.109, $P = 0.001$), but multivariate analysis including CSF RPR displayed no significantly difference in gender between two groups ($P = 0.150$), which was different from previous studies reporting that the incidence of SNS was higher in males than females [4,12]. To clarify the difference between our findings and prior research, we conducted further analysis and identified CSF RPR as a potential mediator variable. Our hypothesis suggested that CSF RPR might directly contribute to the development of neurosyphilis and subsequently influence the outcomes of multivariate logistic analysis. However, upon reevaluation and considering the complexities of this relationship, we made the decision to exclude CSF RPR from the analysis. Following this adjustment, our multivariate analysis indicated that being male remained an independent risk factor for SNS (OR = 2.187, $P = 0.009$) (Table 2). We speculate that this association may be attributed to differences in sexual behavior between men and women. Further exploration into the mechanisms underlying this gender disparity is warranted.

Thirdly, our study demonstrated the patients older than 45 years was a risk factor for SNS with univariate analysis (OR = 2.003, P

Table 2
Univariate and multivariate analysis for predictors of SNS patients.

Factors	Univariate		Multivariate (Including CSF RPR)		Multivariate (Excluding CSF RPR)	
	OR (95%)	*P*-value	OR (95%)	*P*-value	OR (95%)	*P*-value
Sex, male vs female	2.109 (1.338–3.325)	$P = 0.001$	1.592 (0.845–2.998)	$P = 0.150$	2.187 (1.216–3.936)	$P = 0.009$
Age, ≥45 vs < 45, years	2.003 (1.246–3.220)	$P = 0.004$	1.240 (0.659–2.335)	$P = 0.505$	1.454 (0.808–2.616)	$P = 0.212$
Absence of treatment, yes vs no	0.196 (0.121–0.319)	$P < 0.001$	0.322 (0.175–0.592)	$P < 0.001$	0.292 (0.166–0.514)	$P < 0.001$
Pretreatment serum RPR titer	1.014 (1.005–1.022)	$P = 0.001$	1.005 (0.997–1.014)	$P = 0.228$	1.014 (1.004–1.025)	$P = 0.007$
CSF WBC count,/μl	2.104 (1.254–3.529)	$P = 0.005$	0.816 (0.416–1.598)	$P = 0.552$	1.374 (0.755–2.5)	$P = 0.299$
CSF protein concentration, mg/dl	1.742 (0.960–3.152)	$P = 0.067$	0.986 (0.458–2.121)	$P = 0.971$	0.934 (0.453–1.928)	$P = 0.854$
CSF RPR, positive vs negative	8.060 (4.989–13.021)	$P < 0.001$	5.889 (3.191–10.870)	$P < 0.001$	N/A	N/A

Abbreviations: SNS = symptomatic neurosyphilis; RPR = rapid plasma regain; CSF = cerebrospinal fluid; WBC = white blood cells; OR = odds ratio; CI = confidence interval; N/A = not applicable.

= 0.004). However, multivariate analysis including CSF RPR suggested that age older than 45 years was not an independent predictor of SNS ($P = 0.505$). After excluding CSF RPR, multivariate analysis also did not indicate age older than 45 years as an independent predictor ($P = 0.212$) (Table 2), which was different from previous reports. The study of Shi et al. displayed that the age older than 45 years was a correlated risk factor for neurosyphilis [15], but the authors did not furtherly analyzed whether the age older than 45 years was also a risk factor for SNS. In their publication, Li et al. concluded that the age older than 45 years was an independent predictor of SNS [4]. The difference between our and their study was probably due to the patient sample size (249 vs 110) and other unrecognized reasons.

Fourthly, benzathine penicillin G, a very effective drug for syphilis, could stop the natural process of syphilis and reduce the incidence of neurosyphilis [16]. Our study displayed that 216 (86.7%) SNS patients and 86 (56.3%) ANS patients lacked benzathine penicillin therapy. Multivariate analysis shown that lack of benzathine penicillin therapy was associated with SNS (OR = 0.292, $P < 0.001$) (Table 2), which was consistent with previous reports [4,17]. We also found that the median pretreatment serum RPR titer in SNS group (1:32) was significantly higher than ANS group (1:8) ($P < 0.001$) (Table 1). Further analysis excluding CSF RPR indicated that high pretreatment serum RPR titer was an independent risk factor for SNS (OR = 1.014, $P = 0.007$) (Table 2), which was also consistent with previous study [4]. Our results demonstrated that the serum RPR titer level was associated with disease activity and anti-syphilis therapy in the early stage of syphilis was essential to prevent SNS.

Finally, as for the CSF laboratory tests, CSF WBC counts and protein concentration were reported to be indicators of neurosyphilis by previous studies [13,14]. Although CSF RPR was an independent risk factor for SNS, but there were more than a half of ANS patients (87/153, 56.9%) who had negative CSF RPR. So, when diagnosing ANS, other factors such as CSF WBC counts and protein concentration should be taken into account. In our study, we observed significant difference in percentage of CSF WBC abnormality between the two groups (82.7% vs 69.4%, $P = 0.004$) (Table 1), but further analysis displayed that CSF WBC count was not an independent risk factor for SNS ($P = 0.299$), which was consistent with previous studies [4,13]. Our study also observed that the CSF WBC counts in SNS patients were significantly higher than that in ANS patients ($P < 0.001$), indicating more obvious inflammatory activity in SNS patients. The median CSF protein concentration in SNS group was found significantly higher than that in ANS group (68.6 mg/dL vs 54.8 mg/dL, $P < 0.001$), but there was no difference between the proportion of protein abnormality in two groups ($P = 0.065$) (Table 1). Further analysis confirmed that high CSF protein concentration was not an independent risk factor for SNS (OR = 0.934, $P = 0.854$) (Table 2).

In conclusion, our study reveals noteworthy associations between SNS and several key factors, namely male gender and elevated pretreatment serum and CSF RPR titers. Furthermore, our findings suggest that individuals lacking anti-syphilis treatment may face an increased risk of developing symptomatic neurosyphilis. These insights underscore the importance of gender considerations, RPR titers, and treatment status in assessing the risk profile for SNS. However, it is essential to acknowledge the limitations of our research, such as the retrospective nature of the study and potential confounding variables not accounted for. Future research should aim to address these limitations and explore additional factors contributing to the development of SNS, ultimately enhancing our understanding and management of this condition.

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Ethical approval

Reviewed and approved by the ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (#2021-0447), in accordance with the principles of the Declaration of Helsinki.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Wei Li: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jinfang Sun:** Software, Methodology, Formal analysis, Data curation. **Tingting Wang:** Resources, Formal analysis, Data curation. **Yiyuan Liu:** Software, Methodology, Data curation. **Weifang Zhou:** Resources, Methodology, Data curation. **Xiaoyong Man:** Writing – review & editing, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A.H. Ropper, Neurosyphilis, N. Engl. J. Med. 381 (2019) 1358–1363.
[2] F.Z. Du, H.N. Zhang, J.J. Li, et al., Neurosyphilis in China: a systematic review of cases from 2009-2021, Front. Med. 9 (2022) 894841.
[3] J.C. Dombrowski, R. Pedersen, C.M. Marra, R.P. Kerani, M.R. Golden, Prevalence estimates of complicated syphilis, Sex. Transm. Dis. 42 (2015) 702–704.
[4] W. Li, M. Jiang, D. Xu, et al., Clinical and laboratory characteristics of symptomatic and asymptomatic neurosyphilis in HIV-negative patients: a retrospective study of 264 cases, BioMed Res. Int. 2019 (2019) 2426313.
[5] K.G. Ghanem, REVIEW: neurosyphilis: A historical perspective and review, CNS Neurosci. Ther. 16 (2010) e157–e168.
[6] Y. Lu, W. Ke, L. Yang, et al., Clinical prediction and diagnosis of neurosyphilis in HIV-negative patients: a case-control study, BMC Infect. Dis. 19 (2019) 1017.
[7] J.D. Braxton, W. Darlene, Brian Emerson, Elaine W. Flagg, Jeremy Grey, LaZetta Grier, Alesia Harvey, Sarah Kidd, Jennifer Kim, Kristen Kreisel, Eloisa Llata, Kerry Mauk, Rodney J. Presley, Viani Ramirez, Steven Shapiro, St Cyr, Sancta, Mark Stenger, Elizabeth Torrone, Hillard Weinstock, Emily J. Weston, Niketta Womack, Sexually Transmitted Disease Surveillance 2017, 2018.
[8] N. Kissani, S. Nafia, S. Zahlane, N. Louhab, Neurosyphilis: a series of 178 cases at the 3rd-level hospital of Marrakesh (Morocco), Eur. J. Clin. Microbiol. Infect. Dis. 40 (2021) 2129–2135.
[9] O.C. Smibert, S. Abbinga, D.W. Spelman, A.W.J. Jenney, Neurosyphilis: concordance between cerebrospinal fluid analysis and subsequent antibiotic strategy for patients undergoing evaluation of a diagnosis of neurosyphilis, Int. J. Infect. Dis. 82 (2019) 73–76.
[10] C.M. Marra, C.L. Maxwell, S.L. Smith, et al., Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features, J. Infect. Dis. 189 (2004) 369–376.
[11] J. Dumaresq, S. Langevin, S. Gagnon, et al., Clinical prediction and diagnosis of neurosyphilis in HIV-infected patients with early Syphilis, J. Clin. Microbiol. 51 (2013) 4060–4066.
[12] Y. Xiao, M.L. Tong, L.L. Liu, et al., Novel predictors of neurosyphilis among HIV-negative syphilis patients with neurological symptoms: an observational study, BMC Infect. Dis. 17 (2017) 310.
[13] S.N. Cai, J. Long, C. Chen, G. Wan, W.H. Lun, Incidence of asymptomatic neurosyphilis in serofast Chinese syphilis patients, Sci. Rep. 7 (2017) 15456.
[14] N. Levchik, M. Ponomareva, V. Surganova, N. Zilberberg, N. Kungurov, Criteria for the diagnosis of neurosyphilis in cerebrospinal fluid: relationships with intrathecal immunoglobulin synthesis and blood-cerebrospinal fluid barrier dysfunction, Sex. Transm. Dis. 40 (2013) 917–922.
[15] M. Shi, R.R. Peng, Z. Gao, et al., Risk profiles of neurosyphilis in HIV-negative patients with primary, secondary and latent syphilis: implications for clinical intervention, J. Eur. Acad. Dermatol. Venereol. 30 (2016) 659–666.
[16] S. Tuddenham, K.G. Ghanem, Management of adult syphilis: key questions to inform the 2021 centers for disease control and prevention sexually transmitted infections treatment guidelines, Clin. Infect. Dis.: Off. Publ. Infect. Dis. Soc. Am. 74 (2022) S127. S33.
[17] P.G. Choe, J.S. Song, K.H. Song, et al., Usefulness of routine lumbar puncture in non-HIV patients with latent syphilis of unknown duration, Sex. Transm. Infect. 86 (2010) 39–40.