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ORIGINAL ARTICLE

Predictors of unfavorable outcome in neurosyphilis: Multicenter ID-IRI Study

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Abstract

Neurosyphilis (NS) has different clinical manifestations and can appear during any stage of syphilis. We aimed to identify the factors affecting poor outcome in NS patients. Patients with positive cerebrospinal fluid Venereal Disease Research Laboratory test, and positive serological serum treponemal or nontreponemal tests were classified as definite NS. The data of 141 patients with definite NS were submitted from 22 referral centers. Asymptomatic NS, syphilitic meningitis, meningovascular syphilis,

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tabes dorsalis, general paresis, and taboparesis were detected in 22 (15.6%), 67 (47.5%), 13 (9.2%), 10 (7%), 13 (9.2%), and 16 patients (11.3%), respectively. The number of HIV-positive patients was 43 (30.4%). The most common symptoms were headache ($n = 55$, 39%), fatigue ($n = 52$, 36.8%), and altered consciousness (50, 35.4%). Tabetic symptoms were detected in 28 (19.8%), paretic symptoms in 32 (22.6%), and vascular symptoms in 39 patients (27.6%). Eye involvement was detected in 19 of 80 patients (23.7%) who underwent eye examination and ear involvement was detected in eight of 25 patients (32%) who underwent ear examination. Crystallized penicillin was used in 109 (77.3%), procaine penicillin in seven (4.9%), ceftriaxone in 31 (21.9%), and doxycycline in five patients (3.5%). According to multivariate regression analysis, while headache was a protective factor in NS patients, double vision was significantly associated to poor outcome. We concluded that double vision indicated unfavorable outcome among NS patients. A high clinical suspicion is needed for the diagnosis NS. As determined in our study, the presence of headache in syphilitic patients can help in early diagnosis of central nervous system disease.

Keywords Syphilis · Neurosyphilis · Outcome · Cerebrospinal fluid · VDRL

Introduction

Syphilis is a chronic, systemic disease reemerging to have risen in general population in recent years [1, 2]. The causative agent of syphilis, *Treponema pallidum*, could involve the central nervous system at any stage of the disease [3]. Neurosyphilis occurs in 4–10% of patients with syphilis [4]. The meninges, the vasculature, the cranial nerves, and the eyes are involved during early stages; the parenchyma of the brain and the spinal cord are frequently implicated at the tertiary period [5]. It is known that increase in the number of HIV-positive patients contributes to the changes in the clinical spectrum [6].

The incidence of neurosyphilis could not accurately be evaluated because of the widespread use of antibiotics for infections apart from syphilis, and the troubles in reporting patients with sexually transmitted diseases [4, 7]. In a community-based, epidemiological study of 2583 central nervous system infection patients, the number of patients with neurosyphilis was reported to be 24 (0.09%) [8]. Although mortality rates were low in patients with neurosyphilis according to that study, they had serious mental and physical deterioration. There were numerous studies in which the clinical features of patients with neurosyphilis were evaluated [1, 4, 9, 10]. However, to our knowledge, no studies that analyze the factors on the poor outcome of the disease are present. This multicenter, retrospective study aimed to identify the factors affecting poor outcome neurosyphilis patients.

Methods

Design of the study and patient selection

The multicenter and retrospective study was performed to assess the patients with neurosyphilis. The study included hospitalized patients from 22 centers in four countries (Hungary, France, Turkey, USA) between 2000 and 2015, The standard questionnaire was sent to all participant centers and their data were collected in an excel file format. After the submission of individual datasets, final database was formed by merging of all these excel files.

Definitions

Definite neurosyphilis It was diagnosed at any stage of syphilis. If the patients have both of the following criteria:

- Positive cerebrospinal fluid (CSF) Venereal Disease Research Laboratory (VDRL) test
- Positive serum treponemal or nontreponemal serologic test for syphilis (https://wwwn.cdc.gov/nndss/conditions/syphilis/case-definition/2014/)

The patients classified as definite neurosyphilis were included in this study.

Probable neurosyphilis Clinical signs or symptoms consistent with neurosyphilis without an alternative diagnosis, elevated CSF protein or CSF pleocytosis without other reasons, a reactive treponemal or nontreponemal serologic test for syphilis in serum, and a negative VDRL test in CSF, is defined as probable neurosyphilis [11].

Primary syphilis Chancroid and regional lymphadenopathy [12, 13].

Secondary syphilis Disseminate rash and generalized lymphadenopathy [12, 13].

Latent syphilis Those infected with *T. pallidum* without specific signs and symptoms [12, 13].

Tertiary syphilis It included inflammatory lesions of the heart, blood vessels, brain, and nervous system [13].

Table 1 Characteristics of the patients with neurosyphilis

Factor N	Total *n* = 141	Favorable *n* = 76	Unfavorable *n* = 65	*p* value
Age (median; IQR)	47; 40–54	46; 40–55	48; 39–53	0.745
Gender				0.72
Male	123 (87%)	67 (88%)	56 (86%)	
Female	18 (13%)	9 (12%)	9 (14%)	
Immunosuppression[a]				0.012
No	109 (77%)	65 (86%)	44 (68%)	
Yes	32 (23%)	11 (14%)	21 (32%)	
Chronic renal disease				0.35
No	140 (99%)	75 (99%)	65 (100%)	
Yes	1 (1%)	1 (1%)	0 (0%)	
Diabetes mellitus				0.82
No	133 (94%)	72 (95%)	61 (94%)	
Yes	8 (6%)	4 (5%)	4 (6%)	
Drug addiction				0.53
No	120 (85%)	66 (87%)	54 (83%)	
Yes	21 (15%)	10 (13%)	11 (17%)	
Stage of syphilis				0.013
Primer	8 (6%)	8 (11%)	0 (0%)	
Seconder	65 (46%)	31 (41%)	34 (52%)	
Latent	25 (18%)	17 (22%)	8 (12%)	
Tertiary	43 (30%)	20 (26%)	23 (35%)	
Stage of neurosyphilis				0.032
Asymptomatic NS	22 (16%)	7 (9%)	15 (23%)	
Syphilitic meningitis	67 (48%)	41 (54%)	26 (40%)	
Meningovascular NS	13 (9%)	8 (11%)	5 (8%)	
Parenchymal NS	16 (11%)	5 (7%)	11 (17%)	
General paresis	13 (9%)	10 (13%)	3 (5%)	
Tabes dorsalis	10 (7%)	5 (7%)	5 (8%)	
HIV infection				0.16
No	98 (70%)	49 (64%)	49 (75%)	
Yes	43 (30%)	27 (36%)	16 (25%)	

[a] Long term corticosteroid use and malignity

Asymptomatic neurosyphilis If the patient has no neurological symptoms or signs and reactive CSF VDRL test consistent with neurosyphilis, then the case was defined as asymptomatic neurosyphilis [14].

Syphilitic meningitis The patients with headache, confusion, nausea and vomiting, and cranial nerve palsies were classified as syphilitic meningitis [14].

Meningovascular neurosyphilis The patients with symptoms caused by thrombosis, and infarction were classified in this category [14].

Parenchymatous syphilis It manifests general paresis and tabetic neurosyphilis.

General paresis The patients with paretic symptoms were classified in this category [14].

Paretic symptoms Paretic symptoms considered were emotional variability, paranoia, sensory impairment, decline in mental and cognitive abilities, forgetfulness, carelessness, tremor, dementia, and psychiatric disorders [14].

Tabes dorsalis The patients with tabetic symptoms were classified in this category [14].

Tabetic symptoms The following signs and symptoms were considered as tabetic symptoms: sphincter dysfunction, ataxia, Romberg positivity, walking disorder, loss of autonomy, and Argyll-Rrobertson pupil [14, 15].

Table 2 Signs and symptoms of the patients with neurosyphilis

Factor *N*	Total *n* = 141	Favorable *n* = 76	Unfavorable 65	*p* value
Fever				0.48
No	108 (77%)	60 (79%)	48 (74%)	
Yes	33 (23%)	16 (21%)	17 (26%)	
Headache				0.028
No	86 (61%)	40 (53%)	46 (71%)	
Yes	55 (39%)	36 (47%)	19 (29%)	
Nausea/vomiting				0.82
No	116 (82%)	62 (82%)	54 (83%)	
Yes	25 (18%)	14 (18%)	11 (17%)	
Lost weight				0.55
No	124 (88%)	68 (89%)	56 (86%)	
Yes	17 (12%)	8 (11%)	9 (14%)	
Fatigue				0.72
No	89 (63%)	49 (64%)	40 (62%)	
Yes	52 (37%)	27 (36%)	25 (38%)	
Arthralgia				0.28
No	121 (86%)	63 (83%)	58 (89%)	
Yes	20 (14%)	13 (17%)	7 (11%)	
Double vision				0.017
No	123 (87%)	71 (93%)	52 (80%)	
Yes	18 (13%)	5 (7%)	13 (20%)	
Seizures				0.031
No	134 (95%)	75 (99%)	59 (91%)	
Yes	7 (5%)	1 (1%)	6 (9%)	
Tabetic symptoms				0.031
No	113 (80%)	66 (87%)	47 (72%)	
Yes	28 (20%)	10 (13%)	18 (28%)	
Paretic symptoms				0.36
No	109 (77%)	61 (80%)	48 (74%)	
Yes	32 (23%)	15 (20%)	17 (26%)	
Vascular symptoms				0.71
No	102 (72%)	54 (71%)	48 (74%)	
Yes	39 (28%)	22 (29%)	17 (26%)	
Altered consciousness				0.30
No	91 (65%)	52 (68%)	39 (60%)	
Yes	50 (35%)	24 (32%)	26 (40%)	
Sign of meningeal irritation				0.71
No	122 (87%)	65 (86%)	57 (88%)	
Yes	19 (13%)	11 (14%)	8 (12%)	
Cranial nerve palsy				0.26
No	104 (74%)	59 (78%)	45 (69%)	
Yes	37 (26%)	17 (22%)	20 (31%)	
Ocular involvement				0.20
No	61 (43%)	39 (51%)	22 (34%)	
Yes	19 (14%)	9 (12%)	10 (15%)	
Unknown	61 (43%)	28 (37%)	33 (51%)	
Ear involvement				0.28
No	17 (12%)	14 (18%)	3 (5%)	
Yes	8 (6%)	5 (7%)	3 (5%)	
Unknown	116 (82%)	57 (75%)	59 (91%)	
Skin				0.54
No	122 (87%)	67 (88%)	55 (85%)	
Yes	19 (13%)	9 (12%)	10 (15%)	
Lymph nodes				0.053
No	130 (92%)	67 (88%)	63 (97%)	
Yes	11 (8%)	9 (12%)	2 (3%)	

Tabetic symptoms: sphincter dysfunction, ataxia, Romberg positivity, walking disorder, loss of autonomy, Argyll-Robertson pupil. Paretic symptoms: emotional variability, paranoia, sensory impairment, decline in mental and cognitive abilities, forgetfulness, carelessness, tremor, dementia, psychiatric disorder. Vascular symptoms: dizziness, speech impairment, stroke, hemiparesis/hemiplegia, paraparesis/paraplegia, hyperactive reflexes, and hypoesthesia

Ocular syphilis The patients with clinical symptoms and findings consistent with ocular disease at any stage of syphilis were in this category. Visual complaints are loss of vision, blurry vision, painful eye, and eye redness, etc. [16].

Taboparesis The patients with taboparesis have both tabetic and paretic symptoms.

Vascular symptoms Dizziness, speech impairment, stroke, hemiparesis/hemiplegia, paraparesis/paraplegia, hyperactive reflexes, and hypoesthesia were described as vascular symptoms [17].

Unfavorable outcome It was defined as survival with sequela, relapse, or death.

Statistical analysis

Statistical tests were applied by the open-source statistical platform R (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). Significance tests were always double-sided at the level of 0.05. Non-normal distributed continuous variables were presented as median and interquartile ranges. Normality was assessed by the Shapiro-Wilk test. In univariate comparisons of continuous variables Student's *t* test or Wilcoxon rank-sum test and for comparisons of categorical variables chi-square test or, where appropriate, Fisher's exact test were used.

For multivariate model variables were selected according to univariate significance or clinical relevance. Independent variables entered to the final model were selected via a Lasso penalized maximum likelihood model. Final logistic model was fitted after evaluating covariates for collinearity and interactions.

Results

Characteristics of patients

A total of 176 patients were included in this study. Thirty-five patients were classified into probable neurosyphilis category due to negative CSF VDRL test result and were excluded from the study. Finally, the inclusion criteria were met by 141 patients [123 males (87%); median age 47 (interquartile range, 40–54)].

Syphilis was transmitted sexually in 67 patients (47.5%). The route of transmission of the 52.5% was not disclosed by the patients. Seven patients (4.9%) had coexistent focus of syphilis who presented with hepatitis in three patients (2.1%), arteritis in three patients (2.1%), and periostitis in one patient (0.7%).

Patients' characteristics are presented in Table 1. Forty-three of total patients (30%) were detected HIV positives. The average CD4 cell count of these patients was 312.25 ± 257.98 (median: 288; min-max: 2–1130 cells/mm^3). The CD4 cell count of 27 patients was less than 350 cells/mm^3. The mean HIV RNA level was 262,281.1 ± 428,173.5 copies/ml (median: 91338; min-max: 0–2,000,000 copies/ml) in 31 patients (72% of HIV positives) tested for this parameter. The viral load above 100.000 copies/ml was detected in 16 patients (37.2%), and only three patients had undetectable HIV RNA level.

Signs and symptoms

Signs and symptoms of the patients with neurosyphilis are shown in Table 2. Twenty-eight patients (19.8%) had tabetic symptoms. There were walking disorders in 16 patients (11.3%), ataxia in ten patients (7%), Romberg positivity in six patients (4.2%), Argyll-Robertson pupil in five patients (3.5%), sphincter dysfunction in five patients (3.5%), and loss of autonomy in one patient (0.7%). Paretic symptoms were detected in 32 patients (22.6%). Emotional variability in 20 patients (14.1%), forgetfulness in 17 patients (12%), decline in mental and cognitive

Table 3 Cerebrospinal fluid findings of the patients with neurosyphilis

	Favorable $n = 76$	Unfavorable $n = 65$	p value
CSF pressure, *n* (%)			0.198
Unchanged	17 (23.6%)	18 (34.6%)	
Increased	16 (22.2%)	6 (11.5%)	
Unknown	39 (54.2%)	28 (53.8%)	
CSF protein, median [IQR]	79.5 [50.0;112]	67.5 [42.0;125]	0.574
CSF glucose, median [IQR]	52.5 [45.0;60.0]	62.0 [50.8;72.2]	0.001
Blood glucose, median [IQR]	97.0 [89.5;108]	99.0 [85.0;120]	0.627
CSF/serum glucose, median [IQR]	0.52 [0.46;0.61]	0.61 [0.50;0.73]	0.018
CSF leukocyte count, median [IQR]	24.0 [8.50;85.0]	20.0 [3.00;49.0]	0.117

Table 4 Laboratory findings and radiological evaluation of the patients with neurosyphilis

Factor *N*	Favorable *n* = 76	Unfavorable *n* = 65	*p* value
Anemia			0.54
No	30 (39%)	17 (26%)	
Yes	15 (20%)	6 (9%)	
Unknown	31 (41%)	42 (65%)	
Leukopenia (< 4000)			0.54
No	62 (82%)	56 (86%)	
Yes	8 (11%)	5 (8%)	
Unknown	6 (8%)	4 (6%)	
Leukocytosis (> 11,000)			0.16
No	65 (86%)	52 (80%)	
Yes	5 (7%)	9 (14%)	
Unknown	6 (8%)	4 (6%)	
Thrombocytopenia (< 150,000)			0.35
No	40 (53%)	22 (34%)	
Yes	5 (7%)	1 (2%)	
Unknown	31 (41%)	42 (65%)	
High ESR			0.038
No	21 (28%)	17 (26%)	
Yes	18 (24%)	4 (6%)	
	37 (49%)	44 (68%)	
CT/MRI findings			
Normal			0.57
No	20 (26%)	14 (22%)	
Yes	37 (49%)	33 (51%)	
Unknown	19 (25%)	18 (28%)	
Hydrocephalus			0.19
No	53 (70%)	40 (62%)	
Yes	4 (5%)	7 (11%)	
Unknown	19 (25%)	18 (28%)	
Vasculitis (infarct+vasculitis)			0.60
No	45 (59%)	39 (60%)	
Yes	12 (16%)	8 (12%)	
Unknown	19 (25%)	18 (28%)	
Enhancement of the meninges			0.53
No	50 (66%)	43 (66%)	
Yes	7 (9%)	4 (6%)	
Unknown	19 (25%)	18 (28%)	
Edema			0.55
No	53 (70%)	45 (69%)	
Yes	4 (5%)	2 (3%)	
Unknown	19 (25%)	18 (28%)	
Cerebral atrophy			0.81
No	54 (71%)	45 (69%)	
Yes	3 (4%)	2 (3%)	
Unknown	19 (25%)	18 (28%)	

abilities in 13 patients (9.2%), carelessness in ten patients (7%), sensory impairment in eight patients (5.6%), psychiatric disorder in six patients (4.2%), paranoia in five patients (3.5%), tremor in two patients (1.4%), and dementia in two patients (1.4%) were

detected. Vascular symptoms were observed in 39 patients (27.6%) and among these there were dizziness in 26 (18.4%), speech impairment in 15 (10.6%), paraparesis/paraplegia in seven (4.9%), hemiparesis/hemiplegia in four (2.8%), hyperactivity in reflex in four (2.8%), stroke in two (1.4%), and hypoesthesia in only one (0.7%) patient. Coexistent tabetic and paretic symptoms were observed in 17 patients (12%).

Eye examination was performed in 80 patients (56.7%). Ocular involvement caused by syphilis was detected in 19 (23.7%) out of 80 patients evaluated. Optic neuropathy in five patients (6.2%), diminishing visual acuity in five patients (6.2%), uveitis in three patients (3.7%), neuroretinitis in two patients (2.5%), retinal vasculitis in one patient (1.2%), and keratitis in one patient (1.2%). Argyll Robertson pupil was observed in five patients (6.2%). Three neurosyphilis patients infected with HIV had ocular syphilis. Eye examination was performed to 12 out of 18 patients with complaint of double vision. Ocular syphilis was detected in four of these cases.

Ear involvement was detected in eight of 25 patients (32%) who underwent ear examination. Hearing loss in six patients (24%), and tinnitus in three patients (12%) were detected. One patient had both hearing loss and tinnitus.

Laboratory findings and radiological evaluation

CSF findings are shown in Table 3 and laboratory findings are presented in Table 4. Raised CSF pressure was detected in 22 patients (38.5%) among 57 patients who were measured for the CSF pressure. The CSF VDRL test results that appraised as diagnostic criteria were positive in the all of the 141 patients. The median CSF-VDRL titer of 111 patients was four (interquartile range, 2–16). Among the 137 patients tested, all the patients' blood VDRL test results were positive. The median blood-VDRL titer of 111 patients evaluated for this parameter was 64 (interquartile range, 16–128). The blood FTA-ABS (fluorescent treponemal antibody absorption) test was investigated in 78 patients and was positive in all the patients (100%). Six out of 77 (7%) patients tested for blood MHA-TP (microhemagglutination assay) test was positive. The blood TPHA (*Treponema pallidum* hemagglutination) test was made in 125 patients was positive in 55 patients (44%).

One hundred three patients (73%) were imaged with cranial computed tomography (CT)/cranial magnetic

Table 5 Treatment of the patients with neurosyphilis

Factor *N*	Favorable *n* = 76	Unfavorable *n* = 65	*p* value
Crystallized penicillin			0.92
No	17 (22%)	15 (23%)	
Yes	59 (78%)	50 (77%)	
Procaine penicillin			0.55
No	73 (96%)	61 (94%)	
Yes	3 (4%)	4 (6%)	
Ceftriaxone			0.57
No	58 (76%)	52 (80%)	
Yes	18 (24%)	13 (20%)	
Doxycycline			0.77
No	73 (96%)	63 (97%)	
Yes	3 (4%)	2 (3%)	
Steroid			0.004
No	62 (82%)	63 (97%)	
Yes	14 (18%)	2 (3%)	
Mannitol			0.020
No	65 (86%)	63 (97%)	
Yes	11 (14%)	2 (3%)	
Failure of treatment			0.015
No	40 (53%)	15 (23%)	
Yes	1 (1%)	4 (6%)	
	35 (46%)	46 (71%)	
Unfavorable outcome (sequela, relapse or mortality)			< 0.001
No	76 (100%)	0 (0%)	
Yes	0 (0%)	65 (100%)	

Table 6 Multivariate regression analysis of unfavorable outcome data

	OR [95% CIs]	
	Model 1	
Headache	0.32	[0.14–0.73]*
Arthralgia	0.48	[0.14–1.61]
Double vision	5.91	[1.67–20.91]*
Convulsion	11.02	[0.98–123.96]
Tabetic symptoms	1.47	[0.53–4.07]*
Constant	0.96	[0.61–1.54]***
BIC[a]	201.33	
N	141	

[a] Bayesian information criterion

*$p < 0.01$

***$p < 0.001$

resonance imaging (MRI). Seventy patients had normal CT/MRI result.

Treatment

Therapeutic approaches are presented in Table 5. The median duration of crystallized penicillin, procaine penicillin, ceftriaxone, and doxycycline were 14 (interquartile range, 10–14), 10 (interquartile range, 10–14) and 14 (interquartile range, 14–20) days respectively.

Treatment failures were detected in five patients. These were lack of improvement for symptoms and signs in three patients (2%), recurrence of clinical signs in one patient (0.7%), lack of improvement in CSF pleocytosis and recurrence of clinical signs in one patient (0.7%), lack of response to non-treponemal serologic tests in one patient (0.7%). Antibiotic therapy was given once again after treatment failures in two patients (1%).

Follow-up and outcome

The average length of stay in the hospital for patients with neurosyphilis was 15 (interquartile range, 9–21) days. Fifty-nine patients (41.8%) had neurological sequelae as decreased mental status and cognitive disorders in 17 patients (28.8%), hyperactive reflexes in 11 patients (18.6%), convulsions, ataxia in ten patients for each (16.9%), cranial nerve palsies in nine patients (15.2%), loss of vision in seven patients (11.8%), forgetfulness in six patients (10.1%), walking disorders, speech disorders, and hemiparesis/hemiplegia in four patients for each (6.7%), psychiatric disorders in three patients (5%), personality changes, sphincter dysfunction, positive Romberg's sign in two patients for each (3.3%), and emotional variability event in one patient (1.6%) were observed.

Multivariate regression analysis is presented in Table 6 and showed that double vision was significantly associated with unfavorable outcome. Headache was a protective factor for the patients with neurosyphilis.

We did not detect collinearity or interaction effect between the variables of the final model.

Discussion

The clinical presentation of neurosyphilis has been identified to change over the years, and it is reported that this change may be attributed to exposure to antibiotics and increased number of patients co-infected with HIV [18, 19]. In the pre-penicillin era, the commonest form of neurosyphilis was tabes dorsalis, but it is nowadays much rarer [4]. In a 1972 study, Hooshmand et al. found that many patients had unrelated symptoms and were incidentally diagnosed. Abnormal reflex or ocular findings, positive blood, and CSF findings were evaluated consistent with neurosyphilis [7]. Zhang et al. reported that, when analyzing 149 HIV-negative patients, the most frequent clinical presentation was general paresis 38.9% and it was 49% when reviewing 286 patients diagnosed with neurosyphilis in literature [4, 10]. In this study including definite patients with neurosyphilis and HIV-infected cases accounting for 30% of total cases, syphilitic meningitis was identified as the most frequent clinical presentation. It is known that clinical presentation may occasionally overlap in patients with neurosyphilis [5]. The symptoms such as general paresis and tabes dorsalis were observed to coincide in 12% of our cases.

Various types of headache are commonly observed in patients with syphilis, and it may be difficult to differentiate headache syndromes. If the patient with syphilis has headache, neurosyphilis should be remembered [1]. The frequency of headache during the course of neurosyphilis varies around 5–20% in different studies [4, 10, 20]. In our cases including asymptomatic ones, 39% had headaches and this result was higher than it is reported in the literature. Based on our outcome analysis, the presence of headache has a positive effect on prognosis. A study conducted on acute bacterial meningitis showed that lack of headache has a negative effect on prognosis [21]. The other study also indicates that headache is a protective factor for TBM. In this study, the diagnostic criteria of definite TBM were clinical findings of meningitis plus one or more of the following: positive CSF *M. tuberculosis* culture, positive CSF M.*tuberculosis*-PCR analysis, and positive AFB (acid-fast bacilli) in CSF. An inflammation in subarachnoid space during TBM is the result of the immune response to bacteria which results in headache. The absence of headache may indicate weakness of the immune response. Therefore, absence of headache may be a surrogate marker of unfavorable outcome [22].

We determined that the prognosis was poor in those with double vision. Diplopia can be the first symptom of life-threatening neurological or of serious eye diseases. Diplopia is caused by disruption to the system responsible for alignment in the vertical and horizontal planes including supranuclear circuitry, brainstem nucleus, cranial nerves 3, 4, and 6, and their neuromuscular junctions and target muscles as well as responsible for ocular movements. Disruption in vestibular afferents, which control eye movements in response to head motions, also causes diplopia [23]. Although the causes of diplopia were not clarified for all cases, ocular syphilis was recorded in one third of the cases with diplopia. This finding suggests that, although the number of our patients is not enough to draw conclusion, complaints of double vision may be a part of neurological involvement.

Aqueous crystalline penicillin G is the first-choice treatment for neurosyphilis. An alternative treatment includes procaine penicillin G plus probenecid. Although cross-sensitivity between penicillin and ceftriaxone can occur, ceftriaxone could be used in patients with penicillin allergy. The recommended duration for all three treatments is 10–14 days [24]. However, it was reported that treatment with ceftriaxone might have failed in 23% of HIV-infected patients with asymptomatic neurosyphilis or latent syphilis [25]. We found that the effect of ceftriaxone therapy on prognosis did not differ that of penicillin. Given the anaphylactic risk of penicillin therapy and its disadvantages in practice, ceftriaxone appears to be a viable alternative in the treatment of neurosyphilis. Doxycycline 200 mg/day could be administered for 28 days in the treatment of neurosyphilis, despite not having been assessed with systemic studies [26].

In a study, Pratas et al. evaluated to the patients with ocular syphilis both HIV-positive and HIV-negative [27]. They showed that HIV-positive patients had worse prognosis than HIV negatives. In this study performed in the neurosyphilis patients, it is detected that the presence of HIV infection without HIV staging does not have effect on the unfavorable outcome in neurosyphilis patients. Since a neurosyphilis patient with an unknown HIV status can be diagnosed in healthcare settings, particularly in countries with limited resources, we can say that HIV positivity does not affect neurosyphilis prognosis.

Due to NS being a rare infectious disease, this study was designed as a retrospective and a multicenter study as a limitation. Another limitation that may affect the outcome was that 14 patients had experienced syphilis and were treated previously. A prospective study of detailed patient record and continuous follow-up of records will surely be more helpful in future studies.

As said by William Osler, “who knows syphilis, knows medicine,” syphilis likely manifests itself in many different clinical forms [28]. Neurosyphilis may be asymptomatic, however, it may be confronted with tabetic, paretic, or taboparetic symptoms as well. We concluded that headache is a valuable symptom because it draws attention to the central nervous system and that one should keep in mind and be aware that the prognosis may be poor in patients who have double vision.

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Compliance with ethical standards

We have no competing interests to declare. The neurosyphilis study protocol was approved by Fatih Sultan Mehmet Training and Research Hospital in Istanbul.

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