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Neurosyphilis among people with and without HIV infection: A Danish nationwide prospective, population-based cohort study 2015–2021

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SUMMARY

Background: Comparative data on clinical presentation, laboratory characteristics, treatment, and outcome of neurosyphilis (NS) in people living with HIV (PLWH) and NS patients without HIV are scarce.
Methods: Nationwide, population-based, prospective cohort study on all adults with NS diagnosed between 2015 and 2021 at departments of infectious diseases in Denmark.
Results: We identified 108 patients with NS, which equals a yearly incidence of 0.3/100,000 adults. The median age was 49 years, 85 (79%) were male, 43 (40%) were men having sex with men and 20 (22%) were PLWH. Ninety-five (88%) had early NS, 37 (34%) had ocular or ocular and otogenic NS, and 27 (25%) had symptomatic meningitis. Most common symptoms were visual disturbance (44%), skin rash (40%), fatigue (26%) and chancre (17%). Median CSF leukocyte count was 27×10^6 cells/L. PLWH less often had neurological deficits ($p = 0.02$). Unfavorable outcome was observed in 23 (21%) at discharge of whom 0 were PLWH ($p = 0.01$). Among the 88 NS patients without HIV a CSF leukocyte count of $\geq 30 \times 10^6$ cells/L was associated with unfavorable outcome (OR = 3.3 (95% confidence interval: 1.1–10.4)).
Conclusions: PLWH with NS have better outcomes than NS patients without HIV infection.

Introduction

Neurosyphilis (NS) results from the infectious involvement of the central nervous system (CNS) caused by the spirochete *Treponema pallidum*, subspecies pallidum.[1]

The incidence of syphilis decreased significantly in developed countries with the advent of antibiotics and in the early years of the AIDS epidemic. Since year 2000, however, the number of syphilis cases has steadily increased. Current rates of NS are estimated to range from 0.47 to 2.1 cases per 100,000 population, with the highest rates among men having sex with men (MSM) and people living with HIV (PLWH).[1,2] For instance, NS in PLWH in the US is approximately twofold more common than in the background population.[3]

NS can occur at any time in the course of a syphilis infection.[4] Early forms of NS occur from months to a few years after the primary infection and typically affect the cerebrospinal fluid (CSF), meninges,

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and vasculature. Common symptoms of early NS are headache, nausea and vomiting, confusion, neck rigidity and cranial nerve abnormalities (e.g. ocular and auditory abnormalities).[2,5] Meningovascular NS causes ischemia or infarction of the brain or spinal cord due to vasculitis of arteries in the CNS. Yet, early NS may also sometimes be asymptomatic, as alterations in the CSF have been demonstrated in a substantial part of patients with early syphilis without neurological symptoms.[5] Late forms of NS occur within years to decades after infection and comprise general paresis (a progressive dementing illness) and tabes dorsalis characterized by sensory ataxia and lancinating pains.[2] As the clinical features of NS has changed during the last decades, up-to-date evaluations of patients diagnosed with NS are of interest. Furthermore, most previous studies of the clinical presentation and outcome on patients with NS in Europe are restricted to single centers with limited sample sizes. Finally, the impact of HIV on clinical presentation and outcome is not clear.

In order to address these issues, we conducted a nationwide, population-based, prospective cohort study to describe the clinical presentation, CSF findings, antibiotic treatment, and outcome of adults diagnosed with NS at departments of infectious diseases in Denmark from 2015 through 2021 and to elucidate differences in PLWH and NS patients without HIV-infection.

Methods

Setting

The total population of Denmark is 5.9 million people.[6] In Denmark, healthcare is tax-financed and provided to all residents free of charge.

Study population

We used the Danish Study Group of Infections of the Brain (DASGIB) cohort.[7] to identify all adults aged 18 years or more with a first-time episode of NS at a departments of infectious diseases in Denmark from 1st of January 2015 until 31st of December 2021. DASGIB have prospectively enrolled all cases with central nervous system infections from all departments of infectious diseases in Denmark since 2015.[7]

Information on study participants

Baseline information

We calculated yearly incidence of NS by dividing the total number of NS by the total adult population in 2018 (n = 4,615,690) times study period in years. We also calculated the yearly incidence of NS by HIV status, as we assumed that 6800 adults were living with HIV in Denmark in 2018 and that 4,608,890 adults did not have HIV in Denmark in 2018. We extracted the following information on study participants from DASGIB: age, sex, year of diagnosis, overall premorbid function (no physical/cognitive deficits, mild physical/cognitive deficits, moderate physical/cognitive deficits or severe physical/cognitive deficits) and occupational status (Full-time work/study, part-time work/study, unemployed, disability pension/sick leave, retired, not reported). We also extracted information on the most likely mode of syphilis transmission (MSM, bisexual sex, heterosexual sex, heterosexual sex with a sex worker and other including not reported), injection drug use, recent sexual activity with a foreigner during travel abroad, HIV status, other immunosuppression (alcohol abuse, diabetes mellitus, solid or hematological cancer, primary immunodeficiency, or immunosuppressive treatment), and previous syphilis (yes/no). For PLWH, we retrospectively registered most recent viral load (vl) and CD4 cell count and whether they received combination antiretroviral therapy (cART) through chart review. We also extracted patient-reported duration of symptoms.

Disease category

We categorized patients into 1 of 3 categories according to the validity of the diagnosis: definite NS, probable NS and other:

- *Definite NS* was defined as patients with (i) clinical symptoms, (ii) CSF leukocytes > 5×10^6 cells/L and/or CSF protein > 0.5 g/L and (iii) reactive CSF Rapid Plasma Reagin (RPR), reactive CSF Wassermann reaction (WR) or positive intrathecal *T. pallidum* antibody index.
- *Probable NS* was defined as patients with (i) clinical symptoms, (ii) reactive serum treponema test, (iii) CSF leukocytes > 5×10^6 cells/L and/or CSF protein > 0.5 g/L and (iv) other causes for elevated CSF leukocytes/protein have been ruled out (i.e., the principal investigator categorizes the CNS infection as NS).
- *Other NS* was defined as patients reported to have NS in DASGIB by the principal investigators but did not fulfill the criteria for definite or probable NS.

We also categorized the clinical presentation into one of following phenotypes:

- Early NS
  - o asymptomatic meningitis.
  - o symptomatic meningitis.
  - o meningovascularNS.
  - o ocular NS.
  - o otogenic NS.
  - o combined ocular and otogenic NS.
- Late NS
  - o late symptomatic NS with tabes dorsalis.
  - o NS with focal neurological deficits incl. general paresis.
- Other NS.

Outcome at discharge and follow-up is categorized using the Glasgow Outcome Scale (GOS): (1) death; (2) vegetative state; (3) severe sequelae and dependency upon others in daily life; (4) moderate sequelae but with the ability to live independently; and (5) no or mild sequelae.

Statistical analysis

Characteristics at study inclusion. Categorical variables are reported as proportions and percentages, and continuous variables as medians with interquartile rates (IQR). We compared PLWH with NS with other NS patients by use of Chi2 test and Mann-Whitney's *U* test as appropriate.

Outcomes. We defined an unfavorable outcome as a GOS score of 1–4 and compared unfavorable outcome between PLWH with NS and other NS patients. As no PLWH had an unfavorable outcome at discharge or later during follow-up (1, 3 and 6 months after NS), we compared the 2 groups by use of the Chi2 test. In the group of NS patients without HIV, we used logistic regression to compute odds ratios of unfavorable outcome after 1 month for the following a priori defined variables: sex, age ≥ 45 years, CSF leukocyte count (0–29 or ≥ 30×10^6 cells/L), and immunosuppression (other than HIV). We also evaluated serum RPR at 6 months, CSF leukocyte count at 6 months and CSF WR at 6 months. We defined 4 categories for RPR at 6 months: *increased RPR*, *RPR of same level*, *2-fold decrease of RPR* and *4-fold decrease of RPR or return to 0*. We defined 3 categories for CSF leukocytes at 6 months: *≥ 5×10^6 cells/L and ≥ 50% of initial value*, *≥ 5×10^6 cells/L < 50% of initial value* and *< 5×10^6 cells cells/L*. And finally, we defined 3 categories of CSF WR at 6 months *WR still elevated and ≥ 50% of initial value*, *WR still elevated and < 50% of initial*

Table 1
Baseline characteristics.

Characteristics	No. of patients with registered result	All patients n = 108	PLWH n = 20	HIV-uninfected n = 88	P value
Age, years, median (IQR)	108	49 (39–56)	46 (38–59)	49 (40–55)	1.00
Sex, male, n (%)	108	85 (79)	20 (100)	65 (74)	0.01
Year of diagnosis	108				0.21
2015, n (%)		9 (8)	0 (0)	9 (10)	
2016, n (%)		15 (14)	3 (15)	12 (13)	
2017, n (%)		17 (16)	6 (60)	11 (12)	
2018, n (%)		9 (8)	3 (15)	6 (7)	
2019, n (%)		26 (24)	5 (25)	21 (23)	
2020, n (%)		11 (10)	1 (5)	10 (11)	
2021, n (%)		21 (19)	2 (10)	19 (21)	
Physical status before NS	106				0.79
No physical/cognitive deficits, n (%)		82 (77)	15 (75)	67 (78)	
Mild physical/cognitive deficits, n (%)		21 (20)	5 (25)	16 (19)	
Moderate physical/cognitive deficits, n (%)		2 (2)	0 (0)	2 (2)	
Severe physical/cognitive deficits, n (%)		1 (1)	0 (0)	1 (1)	
Occupational status before NS	108				0.20
Full-time work/study, n (%)		62 (57)	12 (60)	50 (57)	
Part-time work/study, n (%)		3 (3)	0 (0)	3 (3)	
Unemployed, n (%)		10 (9)	1 (5)	9 (10)	
Disability pension/sick leave, n (%)		9 (8)	0 (0)	9 (10)	
Retired, n (%)		9 (8)	4 (20)	5 (6)	
Not reported, n (%)		15 (14)	3 (15)	12 (14)	
Risk factors					
Likely mode of transmission (more than one possibility)					
MSM, n (%)	108	43 (40)	17 (85)	26 (30)	0.00
Bisexual sex, n (%)	108	6 (6)	1 (5)	5 (6)	0.90
Heterosexual contact with a sex worker, n (%)	108	5 (5)	0 (0)	5 (6)	0.28
Heterosexual sex, n (%)	108	49 (45)	1 (5)	48 (55)	0.00
Other or not reported, n (%)	108	9 (8)	1 (5)	8 (9)	0.55
Injection drug use, n (%)	108	1 (1)	0 (0)	1 (1)	0.63
Likely transmission outside Denmark, n (%)	105	13 (12)	4 (20)	9 (11)	0.52
Comorbidities[a], n (%)	108	16 (15)	3 (15)	13 (15)	0.98
Previously syphilis within 2 years, n (%)	108	7 (6)	2 (10)	5 (6)	0.48

Abbreviations: MSM, Men having sex with men; PLWH, People living with HIV; HIV, Human immunodeficiency virus; IQR, interquartile range.
[a] Alcohol abuse, diabetes mellitus, solid or hematological cancer (including malignant melanoma, excluding other skin cancers), congenital or acquired immunodeficiency excluding HIV.

value and *WR = 0*. We compared the distribution of these categories between PLWH and other NS patients by use of Chi2 test. We repeated the Chi2 test of unfavorable outcome, RPR at 6 months, CSF leukocyte count at 6 months and CSF W*R* at 6 months in a sensitivity analysis, in which we excluded patients categorized as other NS, to ensure that associations were not driven by potential overlooked alternative diagnoses.

Standard protocol approvals, registrations, and patient consents

The Danish Board of Health (3-3013-2579/1) and The Danish Data Protection Agency (2012-58-0018) have approved the DASGIB study.

Results

We identified 108 adult patients with NS in the DASGIB database including 20 PLWH (19%). This corresponds to an overall yearly incidence of 0.3/100,000 adults in the entire study population, of 42/100,000 adult PLWH and of 0.3/100,000 adults without HIV.

Baseline characteristics

Median age was 49 years (IQR 39–56) and 85 patients (79%) were male (Table 1). Cases were evenly distributed through the study period (Table 1). Most patients had no physical or cognitive deficits prior to NS (n = 82 [77%]) and had full-time work (n = 62 [57%]) (Table 1). Only 1 patient (1%) had reported injection drug use. The primary modes of transmission were heterosexual sex (n = 49 [45%]) and MSM (n = 43 [40%]) and transmission had most often taken place within Denmark (Table 1). Comorbidities associated with immunodeficiency were rare (n = 16 [15%]) (Table 1). For most baseline characteristics, we observed no differences between PLWH and NS patients without HIV infection. More PLWH than NS patients without HIV infection were men and had MSM as likely mode of transmission (Table 1). Of the 20 PLWH, 17 (85%) received cART. Of these, 11 had viral suppression whereas 6 had measurable vl, mostly low-level viremia (data not shown). The 3 patients that did not receive cART were either newly diagnosed or did not wish to take cART. Median CD4 cell count was 682 × 10^6 cells/L (IQR: 401–857 × 10^6 cells/L), and 2 PLWH (10%) had a CD4 cell count below 200 × 10^6 cells/L.

Disease category and clinical findings

Of the 108 patients with NS, 48 (44%) had definite NS, whereas 43 (40%) had probable NS. Ninety-five patients (88%) had early NS with no difference between PLWH and NS patients without HIV infection (Table 2). Median duration of patient-reported symptoms before diagnosis was 30 days (IQR: 10–90 days) with no difference between PLWH and NS patients without HIV infection (Table 2). Most common symptoms were skin rash and visual disturbances. Fewer PLWH had neurological deficits than NS patient without HIV infection, but we did not observe other differences between these 2 groups (Table 2).

Laboratory results and imaging

Most patients had normal levels of blood leukocytes, C-reactive protein (CRP) and alanine aminotransferase (ALAT) (Table 3). The

Table 2
Disease category and other clinical.

Findings	No. of patients with registered result	All patients n = 108	PLWH n = 20	HIV-uninfected n = 88	P value
Diagnosis[a]	108				0.68
Definite NS, n (%)		48 (44)	9 (45)	39 (44)	
Probable NS, n (%)		43 (40)	9 (45)	34 (39)	
Other, n (%)		17 (16)	2 (10)	15 (17)	
Clinical entity	108				0.21
Early syphilis, n (%)		95 (88)	19 (95)	76 (86)	
Asymptomatic meningitis, n (%)		17 (16)	5 (25)	12 (14)	
Symptomatic meningitis, n (%)		27 (25)	5 (25)	22 (24)	
Meningovascular, n (%)		1 (1)	0 (0)	1 (1)	
Ocular NS, n (%)		28 (26)	4 (20)	24 (27)	
Otogenic NS, n (%)		13 (12)	1 (5)	12 (14)	
Ocular and otogenic NS, n (%)		9 (8)	4 (20)	5 (5)	
Late syphilis, n (%)		13 (12)	1 (5)	12 (13)	
Late symptomatic with tabes dorsalis, n (%)		3 (3)	1 (5)	2 (2)	
Focal neurological deficits incl. general paresis, n (%)		10 (9)	0 (0)	10 (11)	
Other neurological syphilitic disease, n (%)		0 (0)	0 (0)	0 (0)	
Other neurological presentations		0 (0)	0 (0)	0 (0)	
Duration of symptoms, days, median (IQR)	89	30 (10–90)	40 (20–60)	30 (10–90)	0.88
Symptoms in patient history					
Genital chancre, n (%)	108	18 (17)	2 (10)	16 (18)	0.38
Skin rash, n (%)	108	43 (40)	6 (30)	37 (42)	0.32
Other chancres, n (%)	108	10 (9)	3 (15)	7 (8)	0.33
Visual disturbances, n (%)	108	48 (44)	9 (45)	39 (44)	0.96
Otogenic symptoms, n (%)	108	29 (27)	5 (25)	24 (27)	0.84
Fatigue, n (%)	108	28 (26)	3 (15)	25 (28)	0.22
Weight-loss, n (%)	108	18 (17)	5 (25)	13 (15)	0.27
Lymph node enlargement, n (%)	108	13 (12)	3 (15)	10 (11)	0.65
Neurological deficits, n (%)	108	28 (26)	1 (5)	27 (31)	0.02
Headache, n (%)	108	12 (11)	4 (20)	8 (9)	0.16
Psychiatric symptoms, n (%)	108	3 (3)	0 (0)	3 (3)	0.40
Cranial nerve palsies, n (%)	108	1 (1)	0 (20)	1 (1)	0.63
Fever (≥ 38C) at admission, n (%)	108	1 (1)	0 (20)	1 (1)	0.63
Other[a], n (%)	108	34 (31)	6 (30)	28 (32)	0.87

[a] Three criteria should be fulfilled for definite NS (i) clinical symptoms, (ii) CSF leukocytes > 5×10^6 cells/L and/or CSF protein > 0.5 g/L and (iii) reactive CSF RPR or reactive CSF W*R* or positive intrathecal *T. pallidum* antibody index. Three criteria should be fulfilled for probable NS (i) clinical symptoms, (ii) reactive serum treponema test, (iii) CSF leukocytes > 5×10^6 cells/L and/or CSF protein > 0.5 g/L and (iv) other causes for elevated CSF leukocytes/protein have been ruled out. Other NS was defined as patients reported to have NS in DASGIB by the principal investigators but did not fulfill the criteria for definite or probable NS.

median level of CSF-leukocytes was 27×10^6 cells/L, the median CSF-lactate was 1.7 mmol/L, the median glucose index was 0.57, and the median CSF protein level was 0.5 g/L (Table 3). We observed no difference in CSF values between PLWH and NS patients without HIV infection. Of the 103 NS patients with non-treponemal test available in serum, 101 (98%) tested positive – most were both W*R* and RPR positive and the median serum-RPR was 64 (IQR: 32–128) (Table 3). Also, 73 (80%) of the 91 patients with one or more available CSF syphilis test tested positive. Brain imaging was carried out in 32/108 (30%) of patients (Table 3). Subarachnoid hemorrhage was demonstrated in 1/7 (14%) PLWH with available brain imagining and 0/25 (0%) NS patients without HIV infection (p = 0.21), but no cases of infarction or vasculitis were demonstrated on brain imagining (data not shown).

Treatment

Most patients were treated for 14 days intravenously (IV) with either ceftriaxone or benzylpenicillin G for the entire treatment course (Table 4). We observed no differences in antibiotic therapy between PLWH and NS patients without HIV infection.

Outcome

At discharge, none of the 20 PLWH had an unfavorable outcome compared with 23 of 88 (26%) among NS patients without HIV infection, p = 0.01 (Table 5). Six months after discharge, 14 (16%) NS patients without HIV infection had unfavorable outcome (Table 5). After 6 months, most patients had a 4-fold decrease in RPR or a return to 0, as well as normalization of CSF leukocytes and CSF W*R*. We observed no differences in the distribution of RPR, CSF leukocyte count, or CSF W*R* at 6 months (Table 5). In the sensitivity analysis, in which we excluded patients categorized as other NS, the results were essentially the same (Supplementary Table 1). Factors associated with an unfavorable outcome 1 month after discharge was a CSF leukocyte count ≥ 30×10^6 cells/L, whereas age, sex, and immunosuppression were not associated with an unfavorable outcome 1 month after discharge (Table 6).

Discussion

In this nationwide, population-based cohort study from the DASGIB cohort, we identified 108 patients with NS of whom approximately 1 out of 5 were PLWH and 40% were MSM. PLWH were more likely to be men, to present without neurological deficits, and to have a favorable outcome. Among NS patients without HIV, meningeal inflammation defined as a CSF leukocyte count > 30×10^6 cells/L was associated with an unfavorable outcome.

Discussion of own results

In this study we tested the hypothesis that PLWH with NS differed from NS patients without HIV. Differences in sex distribution and most likely mode of transmission were as expected. PLWH were less likely to have neurological deficits and an unfavorable outcome. The reasons for this are not entirely clear. One possible explanation is that PLWH are screened frequently. Thus PLWH are offered screening for syphilis at least once yearly.[8] Secondly, awareness of

Table 3
Laboratory results and imaging.

Laboratory results/Imaging	No. of patients with registered result	All patients n = 108	PLWH n = 20	HIV-uninfected n = 88	P value
Serum					
B-leukocytes (10^9 cells/L), median (IQR)	91	8 (6–9)	7 (6–9)	8 (6–9)	0.94
CRP (mg/L), median (IQR)	84	7 (2–19)	9 (3–33)	6 (2–15)	0.19
ALAT (U/L), median (IQR)	79	27 (18–45)	28 (20–61)	26 (18–42)	0.27
CSF					
CSF leukocytes (10^6 cells/L), median (IQR)	107	27 (9–47)	25 (8–67)	27 (10–44)	0.55
Percent mononuclear leukocytes (of total leukocytes), median (IQR)	81	95 (89–98)	95 (85–100)	95 (90–98)	0.82
CSF lactate (mmol/L), median (IQR)	71	1.7 (1.5–1.9)	1.8 (1.4–2.1)	1.7 (1.5–1.9)	0.42
CSF glucose (mmol/L), median (IQR)	104	3.3 (3.0–3.7)	3.4 (3.0–3.9)	3.3 (3.0–3.7)	0.69
Glucose index, median (IQR)	62	0.57 (0.51–0.63)	0.60 (0.49–0.68)	0.57 (0.51–0.63)	0.52
CSF protein (g/L), median (IQR)	105	0.50 (0.37–0.75)	0.66 (0.35–1.06)	0.50 (0.38–0.7)	0.35
Syphilis tests					
In serum					
RPR, median (IQR)	101	64 (32–128)	128 (48–256)	64 (32–128)	0.21
Non-treponemal test positive	103				0.27[a]
No, n (%)		2 (2)	1 (5)	1 (1)	
Yes, n (%)		101 (98)	19 (95)	82 (99)	
WR and RPR positive, n (%)		95 (92)	18 (90)	77 (93)	
Only RPR positive (*WR* negative or not tested), n (%)		4 (4)	1 (5)	3 (4)	
Only *WR* positive (RPR negative or not tested), n (%)		2 (2)	0 (0)	2 (2)	
In CSF					
Any CSF syphilis test positive, n (%)[b]	91	73 (80)	15 (88)	58 (78)	0.36
CSF *WR* positive, n (%)	69	19 (28)	3 (20)	16 (30)	0.46
CSF-*Treponema pallidum* IgG and/or IgM positive, n (%)	81	54 (67)	12 (71)	42 (66)	0.70
Treponema pallidum intrathecal antibody index IgG or IgM positive, n (%)	75	57 (76)	8 (73)	49 (77)	0.78
Imaging					
Head imaging[c] (CT/MRI), n (%)	108	32 (30)	7 (35)	25 (29)	0.56
CT head[c], n (%)	108	16 (15)	4 (20)	12 (14)	0.47
MRI brain[c], n (%)	108	26 (24)	4 (20)	22 (25)	0.64

Abbreviations: ALAT, Alaninetransaminase; *WR*, Wassermann; RPR, Rapid Plasma Reagin; CSF, cerebrospinal fluid; CT, computerized tomography; MRI, Magnetic Resonance Imaging.
[a] Test for positive (*WR* and/or RPR positive) versus negative for individuals (105) who have either a *WR* and/or RPR measurement available.
[b] Any syphilis test positive was defined as either positive CSF *WR* positive and/or positive CSF-Treponema pallidum IgG/IgM and/or positive Treponema pallidum intrathecal antibody index IgG/IgM.
[c] Within the period 1 month before to 1 month after admission date.

syphilis is high and testing possibilities are numerous for PLWH.[8] So although the duration of patient reported symptoms and the proportion of early NS did not differ between PLWH and NS patients without HIV-infection, we speculate that PLWH might be diagnosed earlier in the course of NS resulting in fewer neurological symptoms and a more favorable outcome.[8]

Another important finding is the rather long time between onset of symptoms and diagnosis. This diagnostic delay is worrisome because of the high proportion of unfavorable outcome, and ocular and otogenic involvement. Although initial symptoms of NS might be uncharacteristic,[2] our data might call for heightened awareness of syphilis in general and screening in case of relevant symptoms or exposure.

Treatment guidelines for NS recommend that PLWH should be treated as patients without HIV.[9,10] Treatment with Benzylpenicillin is regarded the gold standard for NS as treponemicidal levels of benzylpenicillin are easy to achieve in the CSF. However, the recommended administration of 4 doses per day requires hospitalization of the patients. Recent data from a retrospective multicenter study of 208 patients with NS suggested that ceftriaxone is similarly

Table 4
Antibiotic therapy.

Parameters	No. of patients with registered result	All patients n = 108	PLWH n = 20	HIV-uninfected n = 88	P value
Length of antibiotic therapy, n (%)	107				0.27
< 14 days		6 (6)	1 (5)	5 (6)	
14 days		76 (71)	18 (90)	58 (67)	
> 14 & < 21 days		9 (8)	0 (0)	9 (10)	
21 days		5 (5)	0 (0)	5 (6)	
> 21 days		11 (10)	1 (5)	10 (11)	
Antibiotic therapy:	107				0.26
Ceftriaxone iv, n (%)		41 (38)	12 (60)	29 (33)	
Doxycycline oral, n (%)		6 (6)	1 (5)	5 (6)	
Benzylpenicillin G iv, n (%)		50 (47)	6 (30)	44 (51)	
Ceftriaxone iv + Doxycycline oral, n (%)		7 (7)	1 (5)	6 (7)	
Benzylpenicillin G iv + Doxycycline oral, n (%)		3 (3)	0 (0)	3 (3)	

Abbreviations: IV, Intravenously.

Table 5
Unfavorable outcome and RPR at different timepoints during follow up. Outcome is categorized using the Glasgow Outcome Scale (GOS).

	No. of patients with registered result	All patients n = 108	PLWH n = 20	HIV-uninfected n = 88	P value[a]
Unfavorable outcome according to GOS					
Unfavorable outcome at discharge, n (%)	107	23 (21)	0 (0)	23 (26)	0.01
Unfavorable outcome 1 month after discharge, n (%)	107	20 (19)	0 (0)	20 (23)	0.02
Unfavorable outcome 3 months after discharge, n (%)	106	14 (13)	0 (0)	14 (16)	0.05
Unfavorable outcome 6 months after discharge, n (%)	106	14 (13)	0 (0)	14 (16)	0.05
RPR 6 months after discharge, n (%)	87				
Increased, n (%)		2 (2)	1 (5)	1 (1)	0.25
Same level, n (%)		6 (7)	3 (16)	3 (4)	
2-fold decrease, n (%)		6 (7)	1 (5)	5 (7)	
4-fold decrease or more (incl negative), n (%)		73 (84)	14 (74)	59 (87)	
CSF leukocytes 6 months after discharge	29				0.90
≥ 5×10^6 cells/L and ≥ 50% of initial value, n (%)		0 (0)	0 (0)	0 (0)	
≥ 5×10^6 cells/L < 50% of initial value, n (%)		8 (28)	1 (25)	7 (28)	
< 5×10^6 cells/L		21 (72)	3 (75)	18 (72)	
CSF WR 6 months after discharge versus initial value	18				0.50
WR still elevated and ≥ 50% of initial value, n (%)		2 (11)	0 (0)	2 (13)	
WR still elevated and < 50% of initial value, n (%)		0 (0)	0 (0)	0 (0)	
WR = 0, n (%)		16 (89)	3 (100)	13 (87)	

[a] P values for unfavorable outcomes are displayed without continuity correction. With continuity correction the p-values were 0.02, 0.04, 0.12 and 0.12.

Table 6
Odds ratios for unfavorable outcome 1 month after discharge among 88 patients with neurosyphilis without HIV.

	OR (95% CI)
Age (years)	
< 45	Reference
≥ 45	0.8 (0.3–2.4)
Sex	
Male	Reference
Female	1.1 (0.3–3.6)
CSF leukocyte count (10^6 cells/L)	
< 30	Reference
≥ 30	3.3 (1.1–10.4)
Immunosuppression	
No	Reference
Yes	3.2 (0.9–11.6)

effective to benzylpenicillin for the treatment of NS regardless of HIV status.[11] We observed no differences in treatment regiments between PLWH and other NS patients, which suggest that this drift towards treatment with ceftriaxone is implemented irrespectively of HIV-status. Lack of serological response to antisyphilitic therapy is a concern for clinicians and theoretically might occur more often in PLWH, although recent data suggest the contrary.[12] In accordance, we demonstrated that the majority of patients had a four-fold decrease in RPR after 6 months and that there was no differences in serological response between PLWH and NS patients without HIV.[12]

Discussion with other studies

In recent studies, the most common form of NS is meningitis, meningovascular and NS with paresis,[13] whereas ocular involvement is particularly frequent among PLWH.[14] Also, NS is common among patients that primarily present with ocular syphilis, which was demonstrated in a recent study of 146 patients with ocular syphilis from South Africa, where 37% were diagnosed with NS and HIV co-infection was present in 52%.[15] The distribution of clinical entities for NS patients without HIV in the current study is in accordance with a previous study from Denmark by Danielsen et al.,[16] whereas the PLWH included in our study had fewer neurological symptoms and a probably a better outcome than described in this study.[16] Another study from Denmark demonstrated that most PLWH with NS were diagnosed with early NS,[17] whereas a study from the Canary Islands of patients with NS without HIV had a higher prevalence of late NS,[13] which are both consistent with our findings. A study from France, that focused on early symptomatic NS, found no differences in outcome between PLWH and NS patients without HIV.[18] To summarize, the total body of evidence including our findings of better outcomes among PLWH suggests that NS may be diagnosed earlier and with milder disease in PLWH. The fact that we did not demonstrate substantial differences in duration of patient-reported symptoms according to HIV status partly contradicts this hypothesis, but patient-reported duration of symptoms might be subject to differential misclassification.

Strengths and limitations

The nationwide, population-based study design with prospective collection of data, and the nearly complete follow-up are advantages of our study. Especially, it is an advantage that we were able to characterize treatment and immune status of PLWH, as HIV infection and immunosuppression might be associated with neurological symptoms in NS.[17] A limitation of our study is the low sensitivity of GOS to describe mild or subtle complications. Another limitation is that some patients with NS, especially those without HIV, are treated at departments of dermatology and therefore not included in the current study. This might result in an underestimation of the incidence of NS and affect the association of outcomes with HIV if patients from departments of infectious diseases differ substantially from those from departments of dermatology. We did register duration of symptoms before diagnosis, but did not specific which symptoms this duration referred to. Tabes dorsalis and general paresis is often associated with a substantial diagnostic delay,[5] and thus duration of symptoms in our study should not be interpreted as time from primary infection to diagnosis. We had access to routine description of brain imagining as reported in the patient chart but were unable to perform second opinion evaluation of these images. Thus, more subtle, and non-specific changed might have been missed. Finally, the number of included cases is rather small. We cannot exclude the possibility that clinically meaningful differences in presentation and outcomes might have not been demonstrated due to lack of power.

Conclusion

This study of 108 patients with NS from the DASGIB cohort demonstrated that PLWH with NS are less likely to present with neurological deficits and have better outcomes than NS patients without HIV infection. This association of HIV with presentation and

outcomes might reflect differences in access to and uptake of syphilis testing. Among NS patients without HIV, a CSF leukocyte count > 30 × 10^6 cells/L was associated with an unfavorable outcome.

Data Availability statement

Data cannot be shared.

Conflict of interests

All authors declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.03.019.

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