Demographics and Clinical Characteristics of Patients with Neurosyphilis in Rhode Island

VINCENT J. MARIANO, MD; SUSAN CU-UVIN, MD; FIZZA S. GILLANI, PhD

ABSTRACT

The incidence of syphilis has been steadily rising throughout the United States over the past decade, including Rhode Island. Neurosyphilis is a manifestation of syphilis involving the central nervous system and can present with a multitude of symptoms. We evaluated all cases of syphilis at a single healthcare system in Rhode Island over a 10.5-year period and identified 33 cases of neurosyphilis (24 confirmed and 9 diagnosed clinically). Neurosyphilis was more common in females, older patients, White/Caucasian patients, and non-Latino patients. Patients with neurosyphilis confirmed by cerebral spinal fluid analysis were more likely to have a higher RPR than patients who did not have neurosyphilis. Six patients with HIV were diagnosed with neurosyphilis and were similar to those with HIV and syphilis except for lower rates of drug use. Given increasing trends, clinicians should be familiar with the diagnosis and management of neurosyphilis.

KEYWORDS: Neurosyphilis, Otosyphilis, Ocular Syphilis, HIV, Rhode Island

BACKGROUND

Syphilis is caused by the bacterial spirochete *Treponema pallidum* and is transmitted both sexually and vertically. Since 2000, there has been an increase in the incidence of primary and secondary syphilis within the United States, in addition to rising rates of congenital syphilis.[1,2] In Rhode Island (RI), there was a 382% increase in the number of infectious syphilis cases from 2012 to 2021.[3] Syphilis has a variable clinical course that is often defined by multiple stages, including primary, secondary, latent, and tertiary. Complications of syphilis include neurosyphilis, syphilis aortitis, hepatic syphilis and other atypical presentations.[4,5,6,7] Neurosyphilis is a manifestation of spirochetal invasion of the central nervous system. This can occur at any stage of infection, but often occurs within days of the initial primary infection. Approximately 1.8% of cases with early syphilis in the United States have neurosyphilis.[8] Early neurosyphilis may be asymptomatic or present with a broad range of symptoms including headache, meningismus, cranial-nerve palsies, and changes in vision or hearing. Late neurosyphilis typically presents decades after primary infection with general paresis, dementia paralytica, and tabes dorsalis; these cases may also present with neuroimaging abnormalities including cerebral gummas and medial temporal lobe enhancements.[1,8,9]

Lack of sensitivity and specificity of both serologic and cerebral spinal fluid (CSF) testing contribute to the difficulty of diagnosing syphilis and neurosyphilis, which necessitates high clinical suspicion for the disease. Sampling of the CSF via a lumbar puncture (LP) is recommended to confirm neurosyphilis.[10] Neurosyphilis is associated with elevated CSF protein (>50mg/dL2) or leukocyte count (>5 white blood cells/mm3).[11] However, neurosyphilis may be diagnosed empirically in clinical practice in some situations where a lumbar puncture may carry excessive risks.

Although late complications of untreated neurosyphilis are likely irreversible, penicillin can help to prevent further progression of neurological complications.[8,12] The treatment for latent syphilis is typically benzathine penicillin G as this has an adequate half-life required to achieve appropriate treponemocidal concentrations over the spirochete's slow dividing cycle. However, benzathine penicillin G does not sufficiently achieve treponemocidal concentrations in the CSF.[13] To treat early and late neurosyphilis, the CDC recommends aqueous crystalline penicillin G 3-4 million units IV every four hours or 18–24 million units every 24 hours as a continuous infusion for 10–14 days.[8] However, there is limited data on neurosyphilis outcomes in the United States.

This study evaluates patients diagnosed with neurosyphilis over a 10.5-year period within our health system to identify characteristics that may be associated with neurosyphilis. We compare cases of neurosyphilis diagnosed empirically or confirmed by CSF analysis and compare patients with confirmed neurosyphilis with those who were found to not have neurosyphilis upon evaluation of CSF studies.

METHODS

This is a retrospective, cross-sectional, observational study of patients who were diagnosed with syphilis with or without neurosyphilis and being managed within the Lifespan Healthcare system. Study participants were identified as patients who tested positive for syphilis (RPR, *Treponema*

antibody, and/or *Treponema pallidium* particle agglutination (TPPA)) between 1/1/2010 and 6/30/2021, were 18 years or older at the time of laboratory tests, and were receiving care in any of the Lifespan facilities in Providence, Rhode Island. Using this criteria, 692 patients were identified with a positive syphilis test during the study period.

All 692 patients were classified into five groups as: Group 1 (all patients diagnosed with syphilis in study timeframe but not neurosyphilis); Group 2 (all patients with neurosyphilis with lumbar puncture (LP) confirmation); Group 3 (all patients who were clinically diagnosed with neurosyphilis based on history alone without confirmatory CSF analysis); Group 4 (all patients with syphilis but required neurosyphilis to be ruled out via CSF analysis), and Group 0 (all patients excluded from the study). Study exclusion criteria included syphilis infection occurring outside of the study time frame (RPR reflecting treated rather than active infection), age of less than 18 at time of syphilis diagnosis, or no available information in the chart to identify if the RPR reflected an active or prior infection.

The EMR search function was used for all 692 patients for the following phrases: "syphilis", "neurosyphilis", "otosyphilis", and "ocular syphilis." Patients who had no record of these in the chart were excluded. The charts of patients with "neurosyphilis", "otosyphilis", and "ocular syphilis" were reviewed in detail for manual data collection. Detailed chart review (beyond demographic information) of the rest of the patients (those who were diagnosed with syphilis in the study timeframe but not diagnosed with neurosyphilis) was not performed.

Patients' age was calculated as of the first positive syphilis lab result date. Demographic variables including gender, race, and ethnicity were collected from the EMR. Some data items related to HIV diseases were taken from The Miriam Hospital Immunology Center Database (ICDB). Manual data collection included binary information (Yes/No) on: prior history of positive RPR, substance use, diagnoses of HIV, pre-exposure prophylaxis for HIV (PrEP) at time of diagnosis, and current or prior history of STIs (gonorrhea, chlamydia, and HCV). "Current" diagnosis of another STI was defined as a positive diagnosis within a 30-day window from the time of syphilis diagnosis. A comprehensive list of neurosyphilis-related symptoms was also collected manually. This included: fever, headache, nausea/vomiting, weight loss, fatigue, arthralgias, vision change, seizures, strokes/TIA, gait abnormalities, dementia, hearing changes, cranial nerve palsy, rash, myalgias, tremors, hair loss, and altered mental status. Laboratory results were also evaluated at the time of diagnosis to assess if hepatic transaminitis was also present (ALT >3 times the upper limit of normal). Treatment administered, and treatment outcomes were also manually collected.

Primary outcomes included incidence and prevalence of neurosyphilis, but the study also evaluated any trends amongst predisposing factors that could be associated with the development of neurosyphilis. For sub-analyses, these groups were further classified as: Group A (all patients who were diagnosed with syphilis but not neurosyphilis) and Group B (all patient diagnosed with neurosyphilis with or without LP confirmation). For second sub-analyses, all patients with neurosyphilis with LP confirmation were compared with patients diagnosed clinically with neurosyphilis without LP confirmation (Group 2 compared with Group 3). Another sub-analysis compared the patients who had neurosyphilis confirmed with an LP with those who required an LP to rule out neurosyphilis (Group 2 compared with Group 4). An additional sub-analysis compared all cases of persons with HIV (PWH) diagnosed with neurosyphilis and PWH diagnosed with other forms of syphilis.

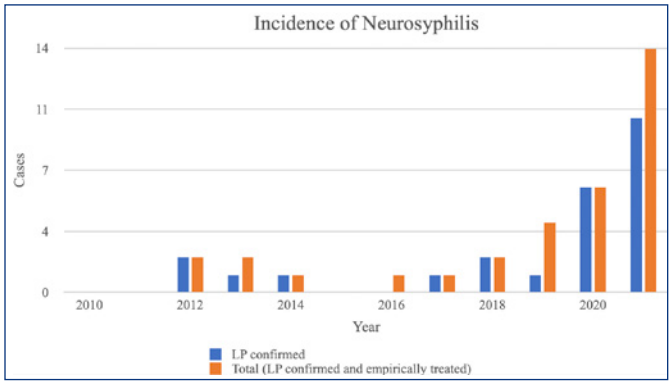
STUDY ANALYSIS

All data was summarized by using descriptive statistics. Bivariate analyses including chi-square, Fisher exact tests, or t-tests were used to assess the marginal effect of demographic and clinical variables on different outcome variables**.** Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Software for chart reviews and manual data entry was created using MS-Access, and all graphs were created using MS Excel software. For all analyses, a P value <.05 was considered significant. The Institutional Review Board of The Miriam Hospital approved the study.

RESULTS

Out of the 692 patients with positive syphilis testing, 94 were excluded either due to lack of information in the chart, no clear diagnosis of syphilis during the study timeframe, or there was a confirmed old/treated syphilis infection as the etiology for the positive RPR. Three patients were excluded as they were younger than 18 at the time of their diagnosis. Of the remaining 598 patients with a diagnosis of syphilis during the study time frame, 8.7% (52) had

Figure 1. Incidence of neurosyphilis throughout the study time frame.



LP: lumbar puncture

symptoms concerning for neurosyphilis. Of these 52, nine patients were treated empirically for neurosyphilis without CSF analysis for confirmation (either the risks of a lumbar puncture to rule out neurosyphilis were felt to be too high or the clinical suspicion for neurosyphilis was high enough that the patient was empirically treated). Of the 43 patients who underwent a lumbar puncture, neurosyphilis was diagnosed/confirmed in 24 patients and ruled out in 19 patients. In total, 33 patients were treated for neurosyphilis and 568 were treated for non-neurosyphilis syphilis. The incidence of neurosyphilis was low until 2019, with a precipitous rise after that (**Figure 1**). The majority of these neurosyphilis cases (42.42%) occurred during the last six months of the study in early 2021.

The characteristics of patients diagnosed with either syphilis or neurosyphilis are detailed in **Table 1**. The average age of patients with syphilis was 38 years (median 33 years, range 18-100 years) compared to 53 years (median 47 years, range 18-89 years) for patients with neurosyphilis (p=0.0118). Women were more commonly diagnosed with neurosyphilis than men (OR 2.84, 95% CI 1.27–6.36), although syphilis was much more common in men overall (87.46%). Those with neurosyphilis were more likely to be White/Caucasian and less likely to be Black/African American compared to the syphilis group (p=0.0101). Neurosyphilis was more common in Non-Hispanic/Latino patients in comparison to the syphilis group (p=0.0166).

A total of 43 patients underwent a lumbar puncture to diagnose neurosyphilis (**Table 2a**, **2b**). Neurosyphilis was confirmed in 24 patients and ruled out in 19 patients. The majority of these lumbar punctures occurred during or after 2019 (31/43 (72.09%); 14/19 cases in which neurosyphilis was ruled out and 17/24 cases in which neurosyphilis was confirmed). There were no significant differences between these two groups in regard to age, gender, race, ethnicity, recent/remote STI diagnosis, HIV status, use of PrEP, drug use, or MSM status. A prior history of syphilis was more common among patients in which neurosyphilis was ruled out by CSF analysis than those for whom it was confirmed (63.16% compared to 29.17%, p=0.0258). RPR values for those with neurosyphilis were higher. Those diagnosed with neurosyphilis were more likely to have a positive CSF FTA (p=<0.0001) and VDRL (p=0.0023). CSF protein was higher in patients diagnosed with neurosyphilis (62.00 compared to 39.42, p=0.0089), but CSF glucose and WBC were not significantly different. The spectrum of presenting symptoms for the two groups are outlined in **Table 2b**. The most common symptom in Group 4 was headaches (47.36%). The most common symptoms for Group 2 were headaches and vision changes (seen in 37.50% of patients). Symptoms were more likely to fully resolve for the syphilis group compared to neurosyphilis (p=0.0045).

Among the patients diagnosed with neurosyphilis (33), nine (27.27%) were diagnosed clinically without CSF analysis (**Table 3a, 3b**). There were no significant differences between these groups except that symptom resolution after treatment was less common in the confirmed neurosyphilis group (p=0.0088). Most (29/33, 87.88%) of the patients with neurosyphilis were treated with a continuous infusion of penicillin G; the duration was usually 14 days (27/29, 93.10%) with only two patients receiving 10 days of IV penicillin G. One of the patients treated empirically received doxycycline 100mg twice daily for 30 days. One of the patients with confirmed neurosyphilis was treated with ceftriaxone 1g IV daily for 14 days; another was treated with doxycycline 200mg twice daily for 28 days; another was treated with intramuscular penicillin G weekly for three weeks followed by a 60-day course of doxycycline 100mg twice daily. The most common symptoms for those with confirmed neurosyphilis were headaches and vision changes, while the most common symptom for those treated empirically was vision changes followed by altered mental status.

A total of 177 persons with HIV (PWH) were found to be diagnosed with syphilis during the study time frame. Six

Table 1. Characteristics of patients with syphilis compared to those with neurosyphilis

Characteristics	Total	Syphilis (Group A)	Neurosyphilis (Group B)	P-Values
Total Patients	598 (100.00)	565 (94.48)	33 (5.52)	
Age (in years) at Syphilis Diagnoses				0.0118**
Mean Age [Min, Max, STD]	39 [18–100, 15]	38 [18–100, 14]	53 [18–89, 19]	
Median Age [IQR]	34 [20]	33 [19]	47 [29]	
Gender				0.0086
Male	523 (87.46)	499 (95.41)	24 (4.59)	
Female	75 (12.54)	66 (88.00)	9 (12.00)	
Race				0.0101*
Black or African American	113 (18.90)	110 (97.35)	3 (2.65)	
White or Caucasian	326 (54.52)	305 (93.56)	21 (6.44)	
All Others	159 (26.59)	150 (94.34)	9 (5.66)	
Ethnicity				0.0166*
Hispanics or Latino	157 (26.25)	151 (96.18)	6 (3.82)	
Not Hispanic or Latino	414 (69.23)	387 (93.48)	27 (6.52)	
Unknown-Others	27 (4.52)	27 (100.00)	0 (0.00)	

Race: All Others include, American Indian or Alaska (5), Asian (10), Native Hawaiian or Other (1), Other (123), Patient Refused (7), Unknown (13)
Ethnicity: Unknown-Others include, Patient Refused (11), Unknown (16)

Table 2a. Characteristics of patients who required lumbar punctures for further assessment to diagnose or rule out neurosyphilis

Characteristics	Total	Non-Neurosyphilis (Group 4)	Neurosyphilis (Group 2)	P-Values
Total Patients	43 (100.00)	19 (44.19)	24 (55.81)	
Age at Syphilis Diagnosis				0.7117
Mean [Min, Max, STD]	52 [18–89, 20]	52 [24–85, 21]	52 [18–89, 19]	
Median [IQR]	47 [34)	54 [40]	47 [25]	
Gender				0.2721*
Male	32 (74.42)	14 (43.75)	18 (56.25)	
Female	11 (25.58)	5 (45.45)	6 (54.55)	
Race				0.0882*
Black or African American	6 (13.95)	3 (50.00)	3 (50.00)	
White or Caucasian	25 (58.14)	11 (44.00)	14 (56.00)	
All Others	12 (27.91)	5 (41.67)	7 (58.33)	
Ethnicity				0.0878*
Hispanics or Latino	13 (30.23)	8 (61.54)	5 (38.46)	
Not Hispanic or Latino	30 (69.77)	11 (36.67)	19 (63.33)	
Prior Syphilis				0.0258
Yes	19 (44.19)	12 (63.16)	7 (36.84)	
No	24 (55.81)	7 (29.17)	17 (70.83)	
STI Any History				0.3195*
Yes	7 (16.28)	3 (42.86)	4 (57.14)	
No	36 (83.72)	16 (44.44)	20 (55.56)	
Any Drug Use History (Drug use + IVDU)				0.2840*
Yes	8 (18.60)	4 (50.00)	4 (50.00)	
No	35 (81.40)	15 (42.86)	20 (57.14)	
HIV				0.2578
Yes	10 (23.26)	5 (50.00)	5 (50.00)	
No	33 (76.74)	14 (42.42)	19 (57.58)	
Use of PrEP if HIV Negative				0.5581*
Yes	1 (2.33)	0 (0.00)	1 (100.00)	
No	42 (97.67)	19 (51.35)	18 (48.65)	
MSM				0.2240
Yes	17 (53.13)	6 (35.29)	11 (64.71)	
No	15 (46.88)	8 (53.33)	7 (46.67)	
Serum RPR (Median, 25th Percentile-75th Percentile)	1:16 (1:2–1:256)	1:4 (1:2–1:16)	1:128 (1:8–1:512)	<.0.0017

*Fisher's Exact Test

Table 2b. Symptoms of patients who required lumbar punctures for further assessment to diagnose or rule out neurosyphilis

	Total	Non-Neurosyphilis (Group 4)	Neurosyphilis (Group 2)	P-Values
Symptom				
Fever	3 (6.98)	1 (33.33)	2 (66.67)	
Headache	18 (41.86)	9 (50.00)	9 (50.00)	
Nausea/ Vomiting	4 (9.30)	2 (50.00)	2 (50.00)	
Weight Loss	1 (2.33)	0 (0.00)	1 (100.00)	
Fatigue	4 (9.30)	3 (75.00)	1 (25.00)	
Arthralgia	4 (9.30)	2 (50.00)	2 (50.00)	
Vision Changes	11 (25.58)	2 (18.18)	9 (81.81)	
Seizure	3 (6.98)	2 (66.67)	1 (33.33)	
Strokes/TIA	4 (9.30)	2 (50.00)	2 (50.00)	
Gait Abnormalities	8 (18.60)	3 (37.50)	5 (62.50)	
Dementia	11 (25.58)	4 (36.36)	7 (63.63)	
Hearing Changes	4 (9.30)	1 (25.00)	3 (75.00)	
Facial Nerve Palsy	1 (2.33)	0 (0.00)	1 (100.00)	
Rash	8 (18.60)	1 (12.50)	7 (87.50)	
Transaminitis	10 (23.26)	1 (10.00)	9 (90.00)	
Myalgias	5 (11.63)	3 (60.00)	2 (40.00)	
Tremors	2 (4.65)	0 (0.00)	2 (100.00)	
Hair Loss	2 (4.65)	0 (0.00)	2 (100.00)	
Altered Mental Status	9 (20.93)	4 (44.44)	5 (55.56)	
Symptom resolution after treatment				0.0045*
Resolved	15 (34.88)	8 (53.33)	7 (46.67)	
Partially Resolved	5 (11.63)	0 (0.00)	5 (100.00)	
Unresolved	20 (46.51)	10 (50.00)	10 (50.00)	
Unknown	3 (6.98)	1 (33.33)	2 (66.67)	

*Fisher's Exact Test

were diagnosed with neurosyphilis (five confirmed with CSF analysis and one diagnosed clinically). PWH were not more likely to be diagnosed with neurosyphilis compared to syphilis (OR 0.5035 (95% CI: 0.2042–1.2416); p-value 0.1294). There were no significant differences between the groups except for drug use history, with PWH with neurosyphilis being less likely to have any substance use history.

Table 3a. Characteristics of patients treated empirically for neurosyphilis compared to those with confirmed neurosyphilis

Characteristics	Total	Suspected Neurosyphilis Group 3	Confirmed Neurosyphilis Group 2	P-Values
Total Patients	33 (100.00)	9 (27.27)	24 (72.73)	
Age (in years) at Syphilis Diagnoses				0.6334*
Mean Age [Min, Max, STD]	53 [18,89,19]	55 [32,84,21]	52 [18,89,19]	
Median Age [IQR]	47 [29]	59 [33]	47 [25]	
Gender				0.2932*
Male	24 (72.73)	6 (25.00)	18 (75.00)	
Female	9 (27.27)	3 (33.33)	6 (66.67)	
Race				0.1085*
Black or African American	3 (9.09)	0 (0.00)	3 (100.00)	
White or Caucasian	21 (63.64)	7 (33.33)	14 (66.67)	
All Others	9 (27.27)	2 (22.22)	7 (77.78)	
Ethnicity				0.3454*
Hispanics or Latino	6 (18.18)	1 (16.67)	5 (83.33)	
Not Hispanic or Latino	27 (81.82)	8 (29.63)	19 (70.37)	
Prior Syphilis				0.3141*
Yes	10 (30.30)	3 (30.00)	7 (70.00)	
No	23 (69.70)	6 (26.09)	17 (73.91)	
STI Any History				0.4029*
Yes	5 (15.15)	1 (20.00)	4 (80.00)	
No	28 (84.85)	8 (28.57)	20 (71.43)	
Any Drug Use History (Drug use + IVDU)				0.3454*
Yes	6 (18.18)	2 (33.33)	4 (66.67)	
No	27 (81.82)	7 (25.93)	20 (74.07)	
HIV				0.3454*
Yes	6 (18.18)	1 (16.67)	5 (83.33)	
No	27 (81.82)	8 (29.63)	19 (70.37)	
Use of PrEP if HIV Negative				0.4091*
Yes	2 (6.06)	1 (50.00)	1 (50.00)	
No	31 (93.94)	8 (25.81)	23 (74.19)	
MSM				0.3651*
Yes	15 (62.50)	4 (26.67)	11 (73.33)	
No	9 (37.50)	2 (22.22)	7 (77.78)	
Serum RPR (Median, 25th Percentile-75th Percentile)	1:64 (1:8–1:512)	1:64 (1:16–1:512)	1:128 (1:8–1:512)	0.7544

*Fisher's Exact Test

Table 3b. Symptoms of patients treated empirically for neurosyphilis compared to those with lumbar puncture confirmed neurosyphilis

	Total	Suspected Neurosyphilis Group 3	Confirmed Neurosyphilis Group 2	P-Values
Symptom				
Fever	3 (9.09)	1 (33.33)	2 (66.67)	
Headache	11 (33.33)	2 (18.18)	9 (81.81)	
Nausea/ Vomiting	2 (6.06)	0 (0.00)	2 (100.00)	
Weight Loss	1 (3.03)	0 (0.00)	1 (100.00)	
Fatigue	2 (6.06)	1 (50.00)	1 (50.00)	
Arthralgia	3 (9.09)	1 (33.33)	2 (66.67)	
Vision Changes	15 (45.45)	6 (40.00)	9 (60.00)	
Seizure	1 (3.03)	0 (0.00)	1 (100.00)	
Strokes/TIA	2 (6.06)	0 (0.00)	2 (100.00)	
Gait Abnormalities	5 (15.15)	0 (0.00)	5 (100.00)	
Dementia	8 (24.24)	1 (12.50)	7 (87.50)	
Hearing Changes	4 (12.12)	1 (25.00)	3 (75.00)	
Facial Nerve Palsy	1 (3.03)	0 (0.00)	1 (100.00)	
Rash	9 (27.27)	2 (22.22)	7 (77.78)	
Transaminitis	10 (30.30)	1 (10.00)	9 (90.00)	
Myalgias	3 (9.09)	1 (33.33)	2 (66.67)	
Tremors	2 (6.06)	0 (0.00)	2 (100.00)	
Hair Loss	2 (6.06)	0 (0.00)	2 (100.00)	
Altered Mental Status	8 (24.24)	3 (27.50)	5 (62.50)	
Symptom resolution after treatment				0.0088*
Resolved	13 (39.39)	6 (46.15)	7 (53.85)	
Partially Resolved	6 (18.18)	1 (16.67)	5 (83.33)	
Unresolved	11 (33.33)	1 (9.09)	10 (90.90)	
Unknown	3 (9.09)	1 (33.33)	2 (66.67)	

*Fisher's Exact Test

DISCUSSION

This is among the most comprehensive studies of neurosyphilis in the state of Rhode Island. Our retrospective chart review study over a 10.5-year period identified 598 patients with a diagnosis of syphilis and 5.5% (33) with a diagnosis of neurosyphilis. The majority of these neurosyphilis cases (42.42%) occurred at the very end of the observation period, between 1/1/2021 and 6/30/2021. This is consistent with data from the RI Department of Health (RIDOH) reporting a 382% increase in the diagnosis of syphilis since 2012 to

2021, with a particularly sharp increase in 2021 with 328 cases.[3] RIDOH had noted a decrease in syphilis diagnoses in 2020 (186), although this was presumably due to less testing in the setting of the COVID-19 pandemic.

We found that most patients diagnosed with any type of syphilis were predominantly male (87.46%). This is consistent with other studies and data reported by the state health department, with almost 90% of cases of syphilis in 2017 occurring in men, especially MSM.[3,14] However, our study notably found that neurosyphilis was more common among female patients compared to men (OR 2.835). The reason for this is not clear but highlights the need for higher clinical suspicion for neurosyphilis in female patients if they are positive for syphilis. HIV is a known risk factor for development of neurosyphilis, especially in those with low CD4 counts and not on antiretroviral therapy.[15] Our study interestingly found that patients with HIV were not more likely to be diagnosed with neurosyphilis. However, we had a rather low sample size of six patients (18.12% of 33 patients with neurosyphilis). HIV viral loads and CD4 counts were not recorded, but it is possible that the cohort of PWH diagnosed with syphilis were mostly well controlled on antiretroviral therapy, reducing the risk of progression to neurosyphilis. Further analysis of this data should be pursued.

Neurosyphilis can present with a variety of symptoms and can be misdiagnosed as a different neurologic disorder in the absence of high clinical suspicion.[16] In the setting of marked increases in the incidence of syphilis and neurosyphilis over the past few years, further attention is required to identify which patients may be at an increased risk for progression of syphilis to neurosyphilis especially as it can even in the early phases. Otosyphilis was rare with hearing changes only noted in two patients (one treated empirically and another diagnosed by lumbar puncture). Ocular syphilis was more frequent with vision changes reported in 45.45% (15/33), with much higher frequency among the group treated empirically for neurosyphilis (6/9). It should be noted though that CSF examination to diagnose neurosyphilis is not typically recommended if the presenting symptoms are ocular or otic in nature, as approximately 30% of persons with ocular syphilis and at least 30% of persons with otic syphilis will have normal CSF findings.[17,18]

The goal of treatment is to prevent progression of neurologic damage and hopefully reverse symptoms. However, some symptoms of neurosyphilis may remain permanently, especially dementia, tabes dorsalis, and ocular and otic symptoms.[12,19,20] We noted that 39.39% of patients diagnosed with neurosyphilis had full resolution of symptoms, but that 18.18% had only partial improvements and 33.33% had no improvements. Notably, patients who had neurosyphilis confirmed by CSF studies seemed to have poorer outcomes than those diagnosed empirically. This difference could be due to possible overdiagnoses of neurosyphilis among the group diagnosed empirically. Roughly 44% of patients who underwent lumbar puncture to evaluate neurosyphilis were ultimately found to not have neurosyphilis and treated instead for latent syphilis.

After treatment, it is recommended to monitor serum RPR titer to ensure that it decreases four-fold or becomes nonreactive within 12 months as adequate treatment.[8,13] Of note, the response to treatment by serial RPR of syphilis without presumed neurosyphilis can sometimes lead to more diagnostics and diagnosis of neurosyphilis (if RPR does not adequately decrease). This was the case for the PWH who was treated empirically for neurosyphilis in our study; their RPR did not adequately improve after treatment for latent syphilis so they were treated empirically for neurosyphilis after declining a lumbar puncture due to anxiety. This study did not evaluate whether serial RPR titers improved after treatment for neurosyphilis, so it is not possible to assess whether a persistence of symptoms had any association with persistently elevated RPR values. However, none of the patients treated for neurosyphilis were later diagnosed with treatment failure.

Our study has several limitations. We did not perform detailed chart reviews of all patients with syphilis as this was outside the scope of our study. We subsequently were not able to compare certain characteristics of these patients (like drug use, sexual partners, use of PrEP) to those with more detailed chart review. While we were able to identify that the patients were diagnosed with syphilis during the study time frame, we relied on the first date of the syphilis serologic testing to determine the age of diagnosis and were unable to identify cases of re-infection. This likely underestimates the incidence of syphilis in Group 1. Notably though, there were no cases of neurosyphilis re-infections in Groups 2 or 3. Despite these limitations, this remains one of the most comprehensive reviews of neurosyphilis in Rhode Island to date.

In summary, cases of syphilis and neurosyphilis are increasing across the United States, including in Rhode Island. The etiology for this is still unclear. While the most significant increases were seen over the most recent years during the COVID-19 pandemic, data from RIDOH indicates that the rise appeared to begin before the onset of the pandemic. It is possible that there has been increased vigilance for neurosyphilis (as demonstrated by the overall increase in lumbar punctures performed to investigate neurosyphilis from 2019 onward) and that perhaps cases of neurosyphilis were previously being underdiagnosed. Further evaluation is also needed to determine if perhaps there may be a more neurotrophic strain of syphilis circulating within Rhode Island. This study highlights the importance for an ongoing need to maintain high clinical suspicion for neurosyphilis in patients who present with neurologic symptoms with a new diagnosis of syphilis.

References

1. Marra CM. Neurosyphilis. Continuum (Minneap Minn). 2015 Dec;21(6 Neuroinfectious Disease):1714-28.
2. Thean L, Moore A, Nourse C. New trends in congenital syphilis: epidemiology, testing in pregnancy, and management. Curr Opin Infect Dis. 2022 Oct 1;35(5):452-460
3. RHODE ISLAND HIV, Sexually Transmitted Diseases, Viral Hepatitis, and Tuberculosis Surveillance Report: https://health.ri.gov/publications/surveillance/2021/HIVSTD.pdf
4. Garg D, Vibha D, Pandit AK, Srivastava AK. Neurosyphilis presenting as pure cerebellar ataxia: an atypical manifestation. BMJ Case Rep. 2019 Aug 31;12(8):e231058.
5. Son C, Samples D, Brenner A, Floyd J. Osteolytic calvarial lesions as initial presentation of latent neurosyphilis. J Clin Neurosci. 2015 May;22(5):909-10.
6. Skalnaya A, Fominykh V, Ivashchenko R, Averchenkov D, Grazhdantseva L, Frigo N, Negasheva E, Dolya O, Brylev L, Guekht A. Neurosyphilis in the modern era: Literature review and case series. J Clin Neurosci. 2019 Nov;69:67-73.
7. Mejdoubi A, Khoulali M, Raouzi N, Nasri S, Mebrouk Y, Oulali N, Moufid F. Neurosyphilis revealed by compressive cervical spine syphilitic gumma: a case report. Spinal Cord Ser Cases. 2020 Jun 30;6(1):56.
8. Ropper AH. Neurosyphilis. N Engl J Med. 2019 Oct 3;381(14):1358-1363.
9. Gonzalez H, Koralnik IJ, Marra CM. Neurosyphilis. Semin Neurol. 2019 Aug;39(4):448-455.
10. Papp JR, Park IU, Fakile Y, Pereira L, Pillay A, Bolan GA. CDC Laboratory Recommendations for Syphilis Testing, United States, 2024. MMWR Recomm Rep 2024;73(No, RR-1):1-32.
11. Brown DL, Frank JE. Diagnosis and management of syphilis. *Am Fam Physician*. 2003;68(2):283-290.
12. Lasagabaster AM, Guerra OL. Syphilis. Enferm Infecc Microbiol Clin (Engl Ed). 2019 Jun-Jul;37(6):398-404.
13. Clement ME, Okeke NL, Hicks CB. Treatment of syphilis: a systematic review. JAMA. 2014 Nov 12;312(18):1905-17.
14. Junco-Fernández A, Montgomery MC, Crowley C, Bertrand T, Marak TP, Maynard MA, Gummo C, Flanigan TP, Chan PA. Increasing Syphilis in Rhode Island: Return of an Old Foe. R I Med J (2013). 2019 Feb 1;102(1):50-54.
15. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. 2008;22(10):1145-1151.
16. Du FZ, Zhang HN, Li JJ, Zheng ZJ, Zhang X, Zhang RL, Wang QQ. Neurosyphilis in China: A Systematic Review of Cases From 2009-2021. Front Med (Lausanne). 2022 May 13;9:894841.
17. Vadboncoeur J, Labbé AC, Fortin C, et al. Ocular syphilis: case series (2000-2015) from 2 tertiary care centres in Montreal, Canada. *Can J Ophthalmol*. 2020;55(1):30-37.
18. Theeuwen H, Whipple M, Litvack JR. Otosyphilis: Resurgence of an Old Disease. *Laryngoscope*. 2019;129(7):1680-1684.
19. Gu X, Gao Y, Yan Y, et al. The importance of proper and prompt treatment of ocular syphilis: a lesson from permanent vision loss in 52 eyes. *J Eur Acad Dermatol Venereol*. 2020;34(7):1569-1578.
20. Gleich LL, Linstrom CJ, Kimmelman CP. Otosyphilis: a diagnostic and therapeutic dilemma. *Laryngoscope*. 1992;102(11):1255-1259.

Authors

Vincent J. Mariano, MD, Departments of Infectious Disease and General Medicine and Community Health, Baystate Health, Springfield, MA.

Susan Cu-Uvin, MD, Division of Infectious Diseases, Warren Alpert Medical School of Brown University, The Miriam Hospital, Providence, RI.

Fizza S. Gillani, PhD, Division of Infectious Diseases, Warren Alpert Medical School of Brown University, The Miriam Hospital, Providence, RI.

Acknowledgments

This work was supported in part by the Providence-Boston (CFAR) Center for AIDS Research, (P30AI042853). We would like to acknowledge Jad Aridi for his assistance with the study idea/proposal and study methods.

Correspondence

Vincent J. Mariano, MD
vincent.mariano@baystatehealth.org