Clinical Infectious Diseases

MAJOR ARTICLE

How Well Do Neurologic Symptoms Identify Individuals With Neurosyphilis?

Arielle P. Davis,[1] Joshua Stern,[2] Lauren Tantalo,[1] Sharon Sahi,[1] Sarah Holte,[2,3] Shelia Dunaway,[4] and Christina M. Marra[1]

[1]Department of Neurology, [2]Department of Global Health, [3]Department of Biostatistics, and [4]Department of Medicine, University of Washington, Seattle

Background. Current guidelines recommend lumbar puncture (LP) in patients with syphilis who have neurologic symptoms.

Methods. A total of 81 human immunodeficiency virus (HIV)-uninfected individuals and 385 HIV-infected individuals enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis underwent LP and a structured symptom history, including assessment of headache; stiff neck; photophobia; ocular inflammation; vision, hearing, or sensory loss; or gait incoordination. Neurosyphilis was defined as a reactive CSF-Venereal Disease Research Laboratory (VDRL) test. Association between categorical variables was assessed using χ^2, Fisher exact test, or logistic regression. Association between continuous and categorical variables was assessed using Mann-Whitney *U* test.

Results. CSF-VDRL was reactive in 20 (24.7%) HIV-uninfected and 68 (17.7%) HIV-infected ($P = .14$) individuals. No symptom was more common in HIV-uninfected individuals with neurosyphilis. Among the HIV-infected, the odds of a reactive CSF-VDRL were higher in those with mild or greater severity photophobia (2.0 [95% confidence interval [CI], 1.1–3.8]; $P = .03$), vision loss (2.3 [1.3–4.1]; $P = .003$), or gait incoordination (2.4 [1.3–4.4]; $P = .006$); or moderate or greater severity hearing loss (3.1 [1.3–7.5]; $P = .01$). Diagnostic specificity of these 4 symptoms for neurosyphilis was high when limited to moderate or greater severity (91.6%–100%); however, the diagnostic sensitivity was low (1.5%–38.1%).

Conclusions. Among HIV-infected patients with syphilis, 4 specific neurologic symptoms are more common in those with a reactive CSF-VDRL. Lack of symptoms does not guarantee that the CSF-VDRL is nonreactive, regardless of HIV status.

Keywords. HIV; neurosyphilis; syphilis; symptoms.

Symptomatic neurosyphilis can occur early or late in the course of infection. In early neurosyphilis, symptomatic meningitis, vision loss, hearing loss, or stroke are most common [1]. The less common, late forms of neurosyphilis include cognitive impairment, sensory loss, and gait incoordination [1]. Current Centers for Disease Control and Prevention (CDC) guidelines recommend a lumbar puncture (LP) in patients with any stage of syphilis who have cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, hearing loss, or ophthalmic disease (uveitis, iritis, neuroretinitis, or optic neuritis) [2]. European guidelines for the management of syphilis provide less specific guidance, suggesting that the clinical scenarios that should dictate an LP in patients with reactive syphilis serology include patients with "clinical neurological symptoms possibly caused by neurosyphilis; clinical ocular symptoms possibly caused by ocular syphilis, or clinical auricular (otologic) symptoms possibly caused by syphilitic otitis" [3].

Received 19 May 2017; editorial decision 26 August 2017; accepted 7 September 2017; published online September 9, 2017.

Correspondence: A. P. Davis, Department of Neurology, Box 359775, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104-2420 USA (apd77@uw.edu).

Clinical Infectious Diseases® 2018;66(3):363–7

DOI: 10.1093/cid/cix799

Neither of the guidelines provide guidance regarding whether some symptoms are more common in patients with neurosyphilis than other symptoms. Our goal in this study was to determine what, if any, specific symptoms in patients with syphilis are more likely in those with neurosyphilis defined as a reactive cerebrospinal fluid (CSF)-Venereal Disease Research Laboratory (VDRL) test. Clinicians could use this information to ensure that those patients with syphilis who are at greatest risk for neurosyphilis based on symptom assessment are targeted for LP. Because some investigators have reported that the clinical manifestations of symptomatic neurosyphilis differ between human immunodeficiency virus (HIV)-infected and HIV-uninfected individuals, we analyzed the 2 groups separately [4, 5].

METHODS

Participants were prospectively enrolled in a study of CSF abnormalities in syphilis conducted in Seattle, Washington, from July 1996 to April 2014 [6]. Eligibility for enrollment included clinical or serological evidence of syphilis and concern by the referring provider or the patient that the patient was at risk for neurosyphilis. Reasons for referral to the study included, but were not restricted to, neurological symptoms or findings, particularly vision or hearing loss; serum rapid plasma reagin (RPR) titer ≥1:32; or, in HIV-infected individuals, peripheral blood CD4+ T cell count ≤350/μL.

Participants underwent a standardized medical history and physical examination, blood draw, and LP performed by a physician or a mid-level provider in a clinic examination room. For 445 (95.5%) visits, the LP and the symptom history were performed on the same day. For the remaining 21 visits, the LP was performed a median of 2 days after the medical history (interquartile range [IQR], 1–7; range 13 days before to 32 days after the medical history). Similarly, the LP and blood draw were on the same day for 93.6% of visits. For the 30 individuals whose LP was not on the same day as the blood draw, the LP was performed a median of 1 day before the blood draw (IQR 1 day before to 3 days after; range 13 days before to 32 days after the blood draw).

Participants were included in this analysis if they had not been treated for the current episode of uncomplicated (nonneurological) syphilis before LP and had a reactive serum RPR. The study protocol was reviewed and approved by the University of Washington Institutional Review Board, and written informed consent was obtained from all study participants.

Syphilis stage was categorized based on CDC guidelines as primary, secondary, early latent, or late latent or syphilis of unknown duration. Medical record review provided results of plasma HIV RNA copy number and peripheral blood CD4+ T lymphocyte count. Only HIV RNA copy number and peripheral blood CD4+ T lymphocyte counts obtained within 90 days of the LP were included in the analysis.

CSF-VDRL tests were performed in a Clinical Laboratory Improvement Amendments–approved hospital clinical laboratory. Serum RPR tests were performed in a research laboratory using published methods [7]. The standardized medical history included assessments of the following neurologic symptoms, which were rated as normal or none, mild, moderate, or severe: headache, stiff neck, photophobia, vision loss, ocular inflammation, hearing loss, sensory loss, and gait incoordination (see Supplementary Table S1). Preexisting symptoms were excluded. Assessment of tinnitus, which was added in July 2010, was only available for 18% of participants and was not considered in the analysis.

Statistical Analyses

Symptoms were categorized as mild or greater in severity (normal/none vs mild and moderate and severe) or moderate or greater in severity (normal/none and mild vs moderate and severe). Neurosyphilis was defined as a reactive CSF-VDRL. We first compared differences in demographics and symptom frequency between HIV-infected and HIV-uninfected participants using χ^2 or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. We then examined associations between each symptom and severity level and CSF-VDRL in HIV-infected and HIV-uninfected participants by logistic regression, which allowed us to express the results as odds ratios (ORs) and to perform multivariate analyses taking into account serum RPR titer (as log base 2) among the HIV-infected group for the symptoms that showed a significant association with CSF-VDRL. Associations between reactive CSF-VDRL, peripheral blood CD4+ T cells, and plasma HIV RNA were assessed using Mann-Whitney *U* test. Associations between the symptoms that were significantly associated with CSF-VDRL reactivity and antiretroviral use were assessed using χ^2 or Fisher exact test. No adjustments were made for multiple comparisons. Diagnostic specificity and sensitivity for the symptoms that were significantly associated with CSF-VDRL in the HIV-infected group were calculated using standard formulae, and differences in sensitivity and specificity were compared using the 2-sample test of proportions (Stata, version 11.2). *P* values < .05 were considered significant.

RESULTS

The characteristics of the 466 individuals included in the analysis are shown in Table 1. Participants were mostly white (70.2%) men (96.6%). Early-stage syphilis was more common in HIV-infected compared to HIV-uninfected participants. Median RPR titer was 1:64. CSF-VDRL was reactive in 20 (24.7%) HIV-uninfected and in 68 (17.7%) HIV-infected individuals; this difference was not statistically significant.

Overall, most participants reported at least 1 of the neurologic symptoms that we assessed. Only 15 (18.5%) HIV-uninfected and 78 (20.3%) HIV-infected participants reported none of the symptoms that we queried. The proportion of participants with each symptom rated as mild or greater in severity is shown in Table 2. Compared to the HIV-infected participants, hearing loss, sensory loss, and gait incoordination were more common in the HIV-uninfected study participants (Table 2).

Table 1. Demographic Characteristics of Study Participants

Characteristic	n (%) or Median (Interquartile Range)		
	HIV-Uninfected n = 81	HIV-Infected n = 385	*P* Value
Male	67 (82.7)	383 (99.5)	<.001
White	48 (59.3)	279 (72.5)	.02
Black	14 (17.3)	60 (15.6)	
Other	19 (23.5)	46 (11.9)	
Age (y)	39 (30–52)	39 (33–45)	NS
Early syphilis Late syphilis	34 (42.0) 47 (58.0)	266 (69.1) 119 (30.9)	<.001
1/Serum rapid plasma reagin titer	64 (4–128)	64 (16–256)	.002
Cerebrospinal fluid–Venereal Disease Research Laboratory reactive	20 (24.7)	68 (17.7)	NS
CD4 count within 90 days	NA	423 (240–554) (n = 351)	NA
HIV RNA within 90 days	NA	1395 (50-55 148) (n = 350)	NA

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable; NS, not significant.

Table 2. Neurologic Symptoms Reported by Study Participants

Symptom	HIV-Uninfected n (%)	HIV-Infected n (%)	*P* Value
Headache[a]	27 (33.3)	149 (39.2), n = 380	NS
Stiff neck[a]	12 (14.8)	59 (15.5), n = 381	NS
Photophobia[a]	13 (16.3), n = 80	64 (17.2), n = 373	NS
Vision loss[a]	44 (56.4), n = 78	179 (47.9), n = 374	NS
Ocular inflammation[a]	19 (23.5)	80 (21.0), n = 381	NS
Hearing loss[a]	24 (30.8), n = 78	63 (17.2), n = 367	.006
Sensory loss[a]	7 (8.8), n = 80	14 (3.7), n = 382	.047
Gait incoordination[a]	21 (26.3), n = 80	63 (16.5), n = 381	.041

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable; NS, not significant.
[a]Mild or greater severity.

Neurosyphilis in Human Immunodeficiency Virus-Uninfected Participants

Twenty (24.7%) of the 81 HIV-uninfected participants had neurosyphilis. Compared to those without neurosyphilis, no clinical symptom, whether characterized as mild or greater in severity or as moderate or greater in severity, was more common in those with neurosyphilis (Table 3 and Supplemental Table S2). As expected based on our previous work [6], serum RPR titer was significantly higher in the HIV-uninfected individuals with neurosyphilis compared to those without neurosyphilis (median [IQR], 1:128 [1:64–1:256] vs 1:16 [1:2–1:64]; $P < .001$).

Neurosyphilis in Human Immunodeficiency Virus-Infected Participants

Sixty-eight (17.7%) of 385 HIV-infected participants had neurosyphilis. Compared to those without neurosyphilis, headache, stiff neck, ocular inflammation, or sensory loss, whether characterized as mild or greater in severity or as moderate or greater in severity, were not more common in those with neurosyphilis. However, compared to those without each individual symptom, the odds of neurosyphilis were significantly higher in HIV-infected individuals with mild or greater severity photophobia, vision loss, or gait incoordination (Table 3). Although the odds of a reactive CSF-VDRL were not significantly higher in those with mild or greater severity hearing loss, the odds of a reactive CSF-VDRL were 3.1 times higher (95% CI, 1.3–7.5; $P = .01$) in HIV-infected individuals with moderate or greater severity hearing loss compared to those with normal or mild hearing loss. There was no significant relationship between peripheral blood CD4+ T cells or plasma HIV RNA concentration within 90 days of the study visit and the neurological symptoms that we assessed. However, antiretroviral use was significantly less common in HIV-infected participants with photophobia than in those without photophobia (18 [34.0%] of 53 vs 145 [60.7%] of 239; $P < .001$). Also, as expected based on our previous work [6], serum RPR titer was significantly higher in HIV-infected participants with a reactive CSF-VDRL compared to those with a nonreactive CSF-VDRL (median [IQR] 1:256 [1:128–1:512] vs 1:64 [1:8–1:128]; $P < .001$). Taking into account serum RPR titer, the odds of a reactive CSF-VDRL remained significantly higher in HIV-infected participants with mild or greater severity vision loss (adjusted OR, 2.2; 95% CI, 1.2–4.0; $P = .01$) and trended toward significance in those with moderate or greater severity hearing loss (adjusted OR, 2.5; 95% CI, 1.0–6.6; $P = .06$).

Table 3. Associations Between Mild or Greater Severity Symptoms and Neurosyphilis

	Odds Ratios (95% Confidence Interval)	
Symptom	HIV-Uninfected	HIV-Infected
Headache[a]	0.6 (0.2–1.8)	0.8 (0.5–1.5)
Stiff neck[a]	1.0 (0.2–4.2)	0.8 (0.4–1.7)
Photophobia[a]	0.5 (0.1–2.5)	2.0 (1.1–3.8)*
Vision loss[a]	1.6 (0.6–4.6)	2.3 (1.3–4.1)**
Ocular inflammation[a]	0.5 (0.1–1.9)	1.1 (0.6–2.0)
Hearing loss[a]	0.8 (0.2–2.4)	1.5 (0.8–2.8)
Sensory loss[a]	1.2 (0.2–6.9)	1.9 (0.6–6.2)
Gait incoordination[a]	1.3 (0.4–3.9)	2.4 (1.3–4.4)***

Abbreviation: HIV, human immunodeficiency virus.
*$P = .03$, **$P = .003$, ***$P = .006$.
[a]Mild or greater severity.

The specificity and sensitivity of photophobia, vision loss, hearing loss, and gait incoordination for neurosyphilis diagnosis in HIV-infected study participants is shown in Table 4. In general, as the symptom severity increased, the specificity increased at the expense of sensitivity.

DISCUSSION

Uncertainty remains regarding which patients with syphilis are most likely to have neurosyphilis and should undergo LP. Current CDC and European guidelines recommend LP for individuals with a wide range of neurologic symptoms. We sought to determine what, if any, specific symptoms in patients with syphilis are more likely in those with neurosyphilis in HIV-uninfected and HIV-infected individuals.

In HIV-infected individuals with syphilis, those with mild or greater severity photophobia, vision loss, gait incoordination,

Table 4. Specificity and Sensitivity of Selected Neurologic Symptoms for Diagnosis of Neurosyphilis in Human Immunodeficiency Virus–Infected Individuals With Syphilis

Symptom	Specificity (95% CI)	Sensitivity (95% CI)
Photophobia[a]	84.8 (80.1–88.8)	26.6 (15.8–37.4)
Photophobia[a]	96.4 (94.3–98.5)	6.3 (0.35–12.3)
Vision loss[a]	55.6 (50.1–61.1)	65.1 (53.3–76.9)
Vision loss[a]	91.6 (88.5–94.7)	38.1 (26.1–50.1)
Hearing loss[a]	83.9 (79.7–88.1)	22.1 (12.2–32.0)
Hearing loss[a]	95.3 (92.9–97.7)	13.2 (5.2–21.2)
Gait incoordination[a]	85.9 (82.0–89.8)	27.9 (17.2–38.6)
Gait incoordination[a]	100 (100.0–100.0)	1.5 (0–4.4)

Abbreviation: CI, confidence interval.
[a]Mild or greater severity.

or moderate or greater severity hearing loss were significantly more likely to have a reactive CSF-VDRL than those without these symptoms. These results suggest that the presence of any of these 4 symptoms should be a criterion for pursuing LP. However, while these 4 symptoms had relatively high diagnostic specificity, they lacked diagnostic sensitivity, meaning that the absence of these symptoms does not predict a nonreactive CSF-VDRL. The explanation for this finding is likely the entity of asymptomatic neurosyphilis, meaning a reactive CSF-VDRL in patients who are asymptomatic. Asymptomatic neurosyphilis is common, particularly in early syphilis, and its clinical significance remains a matter of debate [2].

A higher proportion of HIV-uninfected study participants had neurological symptoms compared to the HIV-infected participants. This finding is likely due to differences in the recommendations for LP in syphilis over the course of our study. Specifically, before 2010, LP was recommended for some asymptomatic HIV-infected individuals with syphilis, but was only recommended for symptomatic HIV-uninfected individuals [8–11]. Despite higher frequency of neurological symptoms, we found that none of the neurologic symptoms that we assessed was more common in HIV-uninfected individuals with a reactive CSF-VDRL. This finding was unexpected and might be explained by small numbers. However, the differences between those with a given symptom who did and did not have a reactive CSF-VDRL were overall very small. The largest difference was seen with mild or greater severity vision loss (11.6%). A sample size of more than 600 individuals would be required to show a significant difference of this magnitude, suggesting that small numbers may not be the entire explanation. Another possible explanation is that among patients with symptomatic neurosyphilis, concomitant syphilitic meningitis may be more common in those who are HIV-infected than in those who are HIV-uninfected. This postulate is supported by other work. For example, a review of 93 HIV-infected and 50 HIV-uninfected individuals with syphilitic uveitis found that the HIV-infected individuals where 1.3 times more likely to have CSF abnormalities than those not infected with HIV [12].

We also considered whether the HIV-infected individuals in our study could have had a confounding explanation for their symptoms other than neurosyphilis, such as HIV itself or opportunistic infections. However, these explanations seem unlikely given that there was no difference in peripheral blood CD4+ T cell or plasma HIV RNA concentrations in HIV-infected individuals with and without neurologic symptoms and the median CD4 count at the time of LP was well above the threshold that would pose risk of opportunistic infection. We did find that photophobia was more common in HIV-infected participants who were not taking antiretroviral agents. Previous studies have documented an increased risk of neurosyphilis in HIV-infected individuals not taking these agents [13, 14].

Limitations of our study should be considered. Neurosyphilis may be diagnosed based on CSF pleocytosis or a reactive CSF-VDRL or both abnormalities. However, CSF pleocytosis in HIV-infected individuals with syphilis may be due to neurosyphilis or HIV or both infections [15]. As such, we defined neurosyphilis solely as a reactive CSF-VDRL to maximize the rigor of our analyses. Although we assessed common symptoms in early and late neurosyphilis, we did not query participants regarding cognitive complaints. However, we screened them with the Mental Alternation test, an oral version of the Trails B test, which has been used to screen for dementia in HIV-infected individuals [16]. We found no association between test score and reactive CSF-VDRL (data not shown). Our participants were mostly HIV-infected white men who have sex with men, in keeping with the demographics of syphilis in our community. Our findings may not be generalizable to other demographic groups. Our overall sample size was large, but the number of individuals with each neurological symptom was relatively small, particularly in the HIV-uninfected group, and we did not account for multiple comparisons. We were unable to assess the clinical relevance of tinnitus due to small numbers. Our study participants were referred because they or their providers were concerned that the participant could have neurosyphilis, which limits the generalizability of our results to those who would have met our entry criteria. However, 80% of our participants had neurological symptoms, which likely would have qualified them for LP.

Our study demonstrates that the presence of mild or greater severity photophobia, vision loss, or gait incoordination or moderate or greater severity hearing loss predicts neurosyphilis, defined as a reactive CSF-VDRL, in HIV-infected individuals with syphilis. However, in HIV-uninfected individuals with syphilis, neurologic symptoms do not predict a reactive CSF-VDRL. Moreover, lack of neurologic symptoms does not predict a nonreactive CSF-VDRL, regardless of HIV status in patients with syphilis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH; grant NS34235).

Potential conflicts of interest. J. S. has received institutional grant funding from the University of Washington/Fred Hutch Center for AIDS Research (P30 AI027757). S. D. has received institutional grant support from the National Institute of Neurological Disorders and Stroke and NIH–National Institute of Allergy and Infectious Diseases. S. H. has received institutional grant support from the University of Washington. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford, **1946**.
2. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep **2015**; 64:1–137.
3. French P, Gomberg M, Janier M, Schmidt B, van Voorst Vader P, Young H. IUSTI: 2008 European guidelines on the management of syphilis. Int J STD AIDS **2009**; 20:300–9.
4. Katz DA, Berger JR. Neurosyphilis in acquired immunodeficiency syndrome. Arch Neurol **1989**; 46:895–8.
5. Gitaí LL, Jaláli PS, Takayanagui OM. Neurosyphilis in the age of AIDS: clinical and laboratory features. Neurol Sci **2009**; 30:465–70.
6. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. J Infect Dis **2004**; 189:369–76.
7. Larsen SA, Pope V, Johnson RE, Kennedy EJ Jr. A Manual of Tests for Syphilis. 9th ed. Washington, DC: American Public Health Association, **1998**.
8. Centers for Disease Control and Prevention. 1993 sexually transmitted diseases treatment guidelines. MMWR Recomm Rep **1993**; 42(RR-14):1–102.
9. Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. MMWR Recomm Rep **1998**; 47(RR-1): 1–111.
10. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR Morb Mortal Wkly Rep **2002**; 51:18–30.
11. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep **2006**; 55(RR-11):1–94.
12. Lee SY, Cheng V, Rodger D, Rao N. Clinical and laboratory characteristics of ocular syphilis: a new face in the era of HIV co-infection. J Ophthalmic Inflamm Infect **2015**; 5:56.
13. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. AIDS **2008**; 22:1145–51.
14. Marra CM, Sahi SK, Tantalo LC, et al. Toll-like receptor polymorphisms are associated with increased neurosyphilis risk. Sex Transm Dis **2014**; 41:440–6.
15. Marra CM, Maxwell CL, Collier AC, Robertson KR, Imrie A. Interpreting cerebrospinal fluid pleocytosis in HIV in the era of potent antiretroviral therapy. BMC Infect Dis **2007**; 7:37.
16. Jones BN, Teng EL, Folstein MF, Harrison KS. A new bedside test of cognition for patients with HIV infection. Ann Intern Med **1993**; 119:1001–4.