

Background

Neurosyphilis presents with notoriously protean clinical manifestations and in a myriad of clinical forms. The challenge is knowing which symptoms in a patient with syphilis should trigger further evaluation for neurosyphilis, including lumbar puncture (LP). Current CDC guidelines recommend LP for individuals with “neurologic symptoms” (1). We sought to determine which clinical symptoms are most predictive of neurosyphilis in a large sample of HIV-infected individuals with syphilis who were referred for LP.

Methods

Participants were prospectively enrolled in a study of cerebrospinal fluid (CSF) abnormalities in syphilis. Eligibility for enrollment included clinical or serological evidence of syphilis and concern by the referring provider that the patient was at risk for neurosyphilis. Risk for neurosyphilis included, but was not restricted to, 1) neurological symptoms or findings, particularly vision or hearing loss; 2) serum Rapid Plasma Reagin (RPR) titer \geq 1:32, or 3) peripheral blood CD4+ T cell count \leq 350/ml. Participants were included in this analysis if they had not been treated for uncomplicated syphilis before study entry and had a reactive serum rapid plasma reagin (RPR) test.

Participants underwent venipuncture and LP. The standardized medical history included assessments of the following neurologic symptoms, which had to be new to be considered: headaches, stiff neck, photophobia, visual loss, ocular inflammation, hearing loss, tinnitus (assessed in only 18% of subjects), sensory loss, and gait incoordination. Subjects rated their symptoms as normal or none, mild, moderate, or severe. Neurosyphilis was rigorously defined as a reactive CSF-VDRL.

Association between categorical variables was assessed by chi-square or fisher exact test and by logistic regression. P-values <0.05 were considered significant. Diagnostic specificity and sensitivity were calculated using standard formulae, and differences in sensitivity and specificity were compared using the two sample test of proportions, Stata version 11.2.

References

1. Workowski KA. Clin Infect Dis. 2015;61(S8):S759-62.

Results

- The 385 participants were mostly white (72.5%) men (99.5%) with early syphilis (70.2%). Median serum RPR titer was 1:64.
- Mild or greater vision loss (47.9%) followed by mild or greater headache (39.2%) were the most commonly reported clinical symptoms.

Table 1. Demographic Characteristics of 385 Study Participants

	n(%) or median (IQR)
Male	383 (99.5)
White	279 (72.5)
Black	60 (15.6)
Other	46 (11.9)
Age	39 (33-45)
1/Serum RPR titer	64 (16-256)
Early syphilis	266 (69.1)
Late syphilis	119 (30.9)
Reactive CSF-VDRL	68 (17.7)
CD4 within 90 days	423 (240-554), n=351
HIV RNA within 90 days	1,395 (50-55,289), n=350

Table 2. Clinical Symptoms Reported

	n(%)
Headache, mild or greater	149 (39.2), n=380
Headache, moderate or greater	72 (18.9), n=380
Stiff neck, mild or greater	59 (15.5), n=381
Stiff neck, moderate or greater	15 (3.9), n=381
Photophobia, mild or greater	64 (17.2), n=373
Photophobia, moderate or greater	15 (4.0), n=373
Vision loss, mild or greater	179 (47.9), n=374
Vision loss, moderate or greater	50 (13.4), n=374
Ocular inflammation, mild or greater	80 (21.0), n=381
Ocular inflammation, moderate or greater	17 (4.5), n=381
Hearing loss, mild or greater	63 (17.2), n=367
Hearing loss, moderate or greater	23 (6.3), n=367
Tinnitus, mild or greater	15 (21.1), n=71
Tinnitus, moderate or greater	5 (7.0), n=71
Sensory loss, mild or greater	14 (3.7), n=382
Sensory loss, moderate or greater	3 (0.8), n=382
Gait incoordination, mild or greater	63 (16.5), n=381
Gait incoordination, moderate or greater	1 (0.3), n=381

Results

- Compared to those without neurosyphilis, the odds of a reactive CSF-VDRL were significantly higher in HIV-infected individuals with mild or greater photophobia, vision loss, gait incoordination, or moderate or greater hearing loss.

Table 3. Associations Between Symptoms and Neurosyphilis (Reactive CSF VDRL)

	Odds ratio (95% CI)
Headache, mild or greater	0.8 (0.5-1.5)
Headache, moderate or greater	0.8 (0.4-1.6)
Stiff neck, mild or greater	0.8 (0.4-1.7)
Stiff neck, moderate or greater	1.2 (0.3-4.2)
Photophobia, mild or greater	2.0 (1.1-3.8)*
Photophobia, moderate or greater	1.8 (0.6-5.9)
Vision loss, mild or greater	2.3 (1.3-4.1)**
Vision loss, moderate or greater	6.7 (3.5-12.9)**
Ocular inflammation, mild or greater	1.1 (0.6-2.0)
Ocular inflammation, moderate or greater	2.7 (0.9-7.5)
Hearing loss, mild or greater	1.5 (0.8-2.8)
Hearing loss, moderate or greater	3.1 (1.3-7.5)**
Tinnitus, mild or greater	0.3 (0.04-2.5)
Tinnitus, moderate or greater	1.3 (0.1-12.3)
Sensory loss, mild or greater	1.9 (0.6-6.2)
Sensory loss, moderate or greater	9.5 (0.8-106.1)
Gait incoordination, mild or greater	2.4 (1.3-4.4)**
Gait incoordination, moderate or greater	--§

*P<0.05, **P≤0.01.

§ Gait incoordination, moderate or greater not calculated due to only 1 subject.

Results

- Serum RPR was significantly higher in participants with a reactive CSF-VDRL compared to those with a non-reactive CSF-VDRL. Taking into account serum RPR titer, the odds of a reactive CSF-VDRL remained significantly higher in subjects with vision loss (OR 2.2, 95% CI 1.2-4.0, P=0.01) and trended toward significance in those with moderate or greater hearing loss (OR 2.5, 95% CI 1.0-6.6, P=0.06).
- In general, as the severity of photophobia, vision loss, hearing loss, and gait incoordination increased, the specificity increased but at the expense of sensitivity.

Table 4. Specificity and Sensitivity of Neurologic Symptoms for Diagnosis of Neurosyphilis (Reactive CSF VDRL)

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

Summary

- **We sought to identify whether specific symptoms were more predictive than others for identifying neurosyphilis in HIV-infected individuals.**
- **HIV-infected participants with mild or greater photophobia, vision loss, gait incoordination, and moderate or greater hearing loss were significantly more likely to have a reactive CSF-VDRL than those without these symptoms, suggesting the presence of any of these four symptoms should be a criterion for pursuing a LP.**
- **While these latter 4 symptoms had high specificity when limited to moderate or greater severity of the symptoms, they were insensitive. Lack of neurologic symptoms in HIV-infected patients with syphilis should not reassure clinicians that their patients do not have neurosyphilis.**

Financial Support

This work was supported by NIH/NINDS NS34235.