Lumbar Puncture in HIV-Infected Patients with Syphilis and No Neurologic Symptoms

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Background. The decision to perform lumbar puncture in patients with asymptomatic human immunodeficiency virus (HIV) infection and syphilis is controversial. The Centers for Disease Control and Prevention recommend certain criteria that warrant lumbar puncture. Here, we assess the performance of these criteria for detecting asymptomatic neurosyphilis (ANS).

Methods. Eligible subjects consisted of all patients with concurrent HIV infection and syphilis in a prospective clinical cohort who had no neurologic symptoms at the time of lumbar puncture. We retrospectively applied different stratification criteria to calculate the performance of lumbar puncture in detecting ANS: (1) lumbar puncture in patients with late latent syphilis or syphilis of an unknown duration, regardless of the CD4 cell count or rapid plasma reagin titer; (2) lumbar puncture if the CD4 cell count was ≤350 cells/mL and/or the rapid plasma reagin titer was ≥1:32, regardless of the syphilis stage; and (3) lumbar puncture in the context of serologic nonresponse to syphilis therapy.

Results. Two hundred two of 231 patients with syphilis did not have neurologic symptoms. Immediate lumbar puncture was performed for 46 patients, and 10 cases (22%) of ANS were detected. With use of the first criterion, 2 (14%) of 10 cases of ANS in patients with early-stage syphilis would have been missed (sensitivity, 80% [95% confidence interval {CI}, 44%–97%]; specificity, 76% [95% CI, 60%–89%]). Criterion 2 would not have missed any cases of ANS (sensitivity, 100% [95% CI, 70%–100%]; specificity, 87% [95% CI, 72%–96%]) but would have required that a lumbar puncture be performed for 88% of patients. Performance of lumbar puncture performed in 13 cases based on serologic nonresponse to syphilis therapy yielded 4 cases (31%) of ANS.

Conclusions. In patients with concurrent HIV infection and syphilis, the use of criteria based on rapid plasma reagin titer and CD4 cell count, instead of stage-based criteria, improved the ability to identify ANS.

In the era before penicillin, patients who received a diagnosis of syphilis—even those without neurologic symptoms—underwent routine lumbar puncture (LP) and examinations of CSF specimens during evaluations for neurosyphilis [1]. Patients with asymptomatic neurosyphilis (ANS) were more likely to develop long-term neurologic sequelae [2, 3] than were those with normal CSF. After World War 2, the rates of neurologic complications of syphilis decreased significantly, despite the use of penicillin formulations that did not achieve treponemalidal levels in the CSF [4]. These observations, coupled with the rapid serologic response of the non-treponemal titers after penicillin treatment [5, 6], led to the abandonment of routine LP in patients without neurologic symptoms. In the 1980s, a number of case reports of neurosyphilis in patients with HIV infection [7–10] prompted the need to revisit the issue of LP for such patients.

There is no disagreement that patients with concurrent syphilis and HIV infection who present with neurologic symptoms should undergo immediate LP to rule out neurosyphilis. There is controversy about the need for LP among patients with concurrent syphilis and HIV infection who do not have neurologic symptoms. For this latter group, the “Sexually Transmitted Diseases Treatment Guidelines, 2006” of the Centers for Disease Control and Prevention (CDC) recommend LP for all
HIV-infected patients who present with late, latent syphilis or syphilis of unknown duration and for all patients with evidence of serologic failure after receipt of syphilis therapy [11].

Previous studies involving HIV-infected patients found an increased risk of neurosyphilis in patients with CD4 cell counts ≤350 cells/mL and rapid plasma reagin (RPR) titers ≥1:32, but those studies included both patients with and patients without neurologic symptoms [12, 13]. We recently reported that HIV-infected patients with syphilis and neurologic symptoms are more likely to have higher RPR titers and lower CD4 cell counts [14]. The 2006 guidelines acknowledge that some experts also recommend adherence to RPR titer- and CD4 cell count–based criteria but that the likelihood that neurosyphilis would be detected with the latter criteria was unknown [11].

As HIV infection evolves into a treatable chronic disease, clinicians need consensus guidelines to help manage syphilis and to evaluate for ANS in this population. Our goal was to compare the sensitivity and specificity of different risk stratification criteria for the diagnosis of ANS among HIV-1–infected patients who were enrolled in a large, longitudinal clinical cohort.

**METHODS**

**Population and data abstraction.** The Johns Hopkins Moore Clinic (Baltimore, MD) provides HIV continuity care to >4000 patients. At enrollment, all patients are offered the opportunity to join the Johns Hopkins HIV Clinical Cohort. A detailed description of this dynamic cohort has been presented elsewhere [15]. Collected clinical data include all clinical, therapeutic, and laboratory parameters. Maintenance of the database and use of its contents for analysis of patient outcomes are approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

**Asymptomatic neurosyphilis.** Patients in the cohort who received a diagnosis of and were treated for syphilis during the period 1990–2006 were eligible for the study. Characteristics of these patients are presented elsewhere [14, 16]. Patients were screened with the nontreponemal RPR test as part of routine clinical care; reactive specimens were confirmed using the fluorescence treponemal antibody absorption test. Syphilis diagnoses were made by clinicians on the basis of CDC criteria [17]. Criteria for the diagnosis of ANS included lack of neurologic signs and symptoms, reactive syphilis serologic test results, and the presence of ≥1 abnormal finding during examination of CSF specimens (WBC count, >10 cells/μL; and/or protein level, >50 mg/dL, without an alternative diagnosis; and/or a reactive CSF Venerable Diseases Research Laboratory [VDRL] test result) [14]. All charts for patients with a syphilis diagnosis were reviewed. Because this was a study of ANS, we excluded patients who had neurologic symptoms at the time of the LP. Patients who underwent LP for reasons other than evaluation of syphilis were excluded from the study. For abstraction of the records, we included the reasons for performing the LP; the timing of the LP, with respect to syphilis diagnosis and treatment; and data on CD4 cell counts and/or a RPR titer 1:32, irrespective of syphilis stage. We also evaluated the yield of detecting ANS for delayed LP performed in response to inadequate serologic response to syphilis therapy. An inadequate serologic response was defined as the lack of a ≥4-fold decrease in the RPR titer ≥12 months after receipt of appropriate therapy for syphilis or a ≥4-fold increase in the RPR titer ≥30 days after receipt of syphilis therapy [11].

**Statistical analysis.** We compared independent means and proportions using the Wilcoxon signed rank test and the χ² test, respectively. We compared paired means and proportions using Student’s paired t test and McNemar’s test, respectively. We used standard definitions to calculate the sensitivity (true-positive results divided by the sum of true-positive and false-negative results) and specificity (true-negative results divided by the sum of true-negative and false-positive results) measures. We evaluated the impact of LP on the risk for subsequent re-treatment of syphilis by using time-to-event statistical models. We used the Andersen-Gill method to adjust for the repeated measures [18]. The proportional hazard assumption with robust variance estimation was tested using scaled Schoenfeld residuals against log of time. P values <.05 were considered to represent statistical significance. Stata software, version 10.1 (Stata Corp.), was used to conduct analyses.

**RESULTS**

During the period 1990–2006, a total of 180 HIV-infected patients received diagnosis of 231 episodes of syphilis. Characteristics of these patients and their clinical courses are presented elsewhere [14, 16]. Of these 231 episodes, 27 cases of symptomatic neurosyphilis and 2 cases of other neurologic conditions that caused symptoms (cryptococcal meningitis and progressive multifocal leukoencephalopathy) were excluded. The remaining 202 did not have neurologic signs or symptoms at the time of syphilis evaluation. The demographic and clinical characteristics of patients with these cases, stratified by LP status, are summarized in table 1.
Table 1. Demographic and clinical characteristics of patients included in the analyses, stratified by lumbar puncture (LP) status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No LP (n = 141)</th>
<th>Immediate LP (n = 48)</th>
<th>Delayed LP (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>51 (36)</td>
<td>16 (33)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Age, mean years (range)</td>
<td>38.6 (23–68)</td>
<td>37.8 (24–55)</td>
<td>38.1 (22–61)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>120 (85)</td>
<td>45 (94)</td>
<td>12 (92)</td>
</tr>
<tr>
<td>White</td>
<td>16 (11)</td>
<td>3 (6)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Risk group for HIV infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>43 (31)</td>
<td>14 (29)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>62 (44)</td>
<td>23 (48)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Injection drug user</td>
<td>48 (34)</td>
<td>22 (46)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Syphilis stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>50 (35)</td>
<td>11 (23)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>LL or UD</td>
<td>91 (65)</td>
<td>37 (77)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>RPR titer, median (IQR)</td>
<td>128 (16–256)</td>
<td>256 (32–1024)</td>
<td>128 (32–512)</td>
</tr>
<tr>
<td>Previous history of syphilis</td>
<td>55 (39)</td>
<td>25 (52)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>CD4 cell count, cells/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>330 (132–501)</td>
<td>264 (130–396)</td>
<td>206 (140–345)</td>
</tr>
<tr>
<td>≤350 cells/mL</td>
<td>55 (39)</td>
<td>30 (63)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>HIV RNA level, median copies/mL (IQR)</td>
<td>16,034 (316–100,726)</td>
<td>3567 (178–63,824)</td>
<td>4276 (348–73,452)</td>
</tr>
<tr>
<td>Use of HAART in previous 6 months</td>
<td>86 (61)</td>
<td>31 (65)</td>
<td>8 (62)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; LL, late latent; MSM, men who have sex with men; RPR, rapid plasma reagin; UD, unknown duration.

Of the 202 cases, LP was performed for 61 (30%), and 14 cases (23%) of ANS were detected. The diagnosis of ANS was based on pleocytosis in 46% of cases, protein level in 58%, and a positive CSF VDRL result in 50%. Only 1 abnormality was noted in 50% of cases (of those, 43% involved isolated pleocytosis, and 57% involved elevated protein levels), 2 abnormalities were noted in 42% of cases, and all 3 abnormalities were noted in 8% of cases. LP was performed for 48 (79%) of 61 cases a median of 1 day (interquartile range, 0–14 days) after syphilis diagnosis. Review of the medical records revealed that the LP was performed because of underlying HIV infection in patients with newly diagnosed syphilis (78%), concern about a high initial RPR titer documented by the health care provider (18%), and pregnancy (4%). Of these 48 cases, 10 (21%) were found to be ANS. The remaining 13 of 61 patients who continued to be neurologically asymptomatic underwent LP a median of 287 days (interquartile range, 100–360 days) after diagnosis and treatment of syphilis. The 2 main reasons were an increasing RPR titer ≥30 days after therapy (48%) or a lack of a ≥4-fold decrease in the RPR titer in response to therapy (52%).

Of the 48 patients who underwent immediate LP, 30 (63%) had a CD4 cell count ≤350 cells/mL, 37 (77%) had a pretreatment RPR titer ≥1:32, 43 (90%) had one or both, and 37 (77%) had late-latent or an unknown duration of syphilis. Figure 1 summarizes the retrospective application of the late-latent stage-based criterion to the entire cohort. Overall, 68% of the cases were late-latent stage at the time of syphilis diagnosis and would have required an LP. Two cases of ANS (or ANS occurring in 18% of cases of early syphilis) would have been missed. As shown in figure 2, application of the CD4 cell count/RPR criteria would have meant that 88% of cases underwent LP, but no cases of ANS would have been missed. If a CD4 cell count ≤350 cells/mL had been used as the sole criterion, 3 cases of ANS would have been missed; if an RPR titer ≥1:32 had been used as the sole criterion, 1 case of ANS would have been missed.

Of the 13 of 61 cases that remained asymptomatic for which delayed LP was performed because of a lack of serologic titer response after therapy for syphilis, 4 (31%) were found to be ANS.

The decision to perform LP was not associated with the likelihood of short-term syphilis re-treatment. After a median of 4 years of follow-up, 38% of patients who were neurologically asymptomatic and did not undergo LP were ultimately retreated for syphilis, compared with 36% of those who did undergo LP (unadjusted hazard ratio, 1.3; 95% CI, 0.7–2.3; \( P = .4 \)).
DISCUSSION

The currently recommended CDC syphilis stage–based criterion may be inadequate if the goal is to identify ANS, to minimize the potential for long-term sequelae. The application of the CD4 cell count– or RPR-based criterion was more sensitive, because it did not miss any cases of ANS. A recent study that included both patients with symptomatic neurosyphilis and patients with asymptomatic neurosyphilis found that use of the RPR-based criterion (RPR titer, ≥1:32) without the CD4 cell count criterion also led to no missed cases of ANS [13]. In our study, which only included asymptomatic patients, use of the RPR titer cutoff without the CD4 cell count criterion would have led to decreased sensitivity and 1 missed case of ANS in a patient with early syphilis who presented with an RPR titer of 1:16 and CD4 cell count of 167 cells/mL.

LP requires additional resources and training and may be difficult to perform in many outpatient settings, such as sexually transmitted diseases clinics where syphilis is commonly diagnosed. In addition, it may be difficult to convince an asymptomatic patient that an LP will contribute to an improved outcome. And lastly, LP is not without complications. In our clinical setting, where it is feasible to schedule an LP, it was performed in less than one-third of cases. A review of the clinic notes (72 charts) in cases in which LP was not performed revealed that patients refused the procedure in 38% of cases. On the remaining charts, the provider had not documented whether LP was even considered.

In our population, the application of either criterion would have led to performance of LP for 70%–90% of syphilis cases. Compared with the stage-based criterion, application of the CD4 cell count/RPR criterion would lead to performance of ~20% more LPs. One alternative to LP is treating coinfected patients with a therapeutic regimen that adequately penetrates the CNS [19, 20]. Intravenous and intramuscular formulations of penicillin readily achieve that goal, but these agents require daily injections over several weeks, making outpatient therapy difficult in many settings. Additional research is warranted that weighs risks of neurologic sequelae, LP, and therapy against close serologic follow-up of the HIV-infected patient with ANS in the HAART era.

The current CDC recommendation that LP be performed for patients with concurrent HIV infection and syphilis whose RPR titers either do not respond appropriately to therapy or whose titers increase after therapy [11] may be the decision rule that identifies the highest number of cases of ANS. In our study, 30% of patients were found to have ANS. We have no way of ascertaining—even indirectly—whether performance of an LP at the time of syphilis diagnosis in these patients would have demonstrated CNS involvement earlier. At the time of syphilis diagnosis, 9 (69%) of 13 patients had late latent syphilis, and 12 patients (92%) had a CD4 cell count ≥350 cells/mL and/or an RPR titer ≥1:32. Of the 4 patients (31%) who subsequently received a diagnosis of ANS, only 2 (50%) had late latent syphilis, although all would have satisfied the CD4 cell count/RPR criterion.

This study has several limitations. First, the criteria to perform LP were applied retrospectively. To try and minimize bias, we reviewed the medical charts of all patients to determine the....
Figure 2. Retrospective application of the second risk stratification criterion, which was based on performance of a lumbar puncture (LP) in patients with a CD4 cell count ≤350 cells/mL and/or a rapid plasma reagin (RPR) titer ≥1:32. ANS, asymptomatic neurosyphilis.

reasons for LP. There were a relatively small number of LPs performed, and we may have missed LPs if they had been performed elsewhere. There are no standard criteria for the diagnosis of neurosyphilis. Only 50% of our cases had positive CSF VDRL results. Moreover, HIV infection may cause CSF abnormalities [21]. No CSF fluorescence treponemal antibody absorption tests were performed. However, we did use criteria that are accepted and that would have led to administration of therapy for neurosyphilis in routine clinical practice.

Our patient population consisted mostly of African American patients with fairly heterogeneous risk factors for syphilis and HIV infection. Thus, the findings are likely to be generalizable to other populations. The re-treatment rates may have been associated with either treatment failure or reinfection; we did not have reliable histories to distinguish one from the other. The ability to determine whether the early LP management strategy has an impact on decreasing long-term morbidity in these patients would have required a much longer follow-up period. Finally, the clinical significance of ANS in the antibiotic era is unclear. Studies conducted in the early part of the 20th century suggested that CSF abnormalities in asymptomatic patients who had either early or late latent syphilis resulted in symptomatic neurosyphilis up to twice as frequently as in those with normal CSF parameters [2, 3]. In the pre-HIV penicillin era, the rates of symptomatic neurosyphilis decreased [4], even as the rates of LP decreased, suggesting that penicillin therapy for early- and late-latent syphilis (in addition to receipt of antibiotics with treponemicidal activity for other indications) may be adequate to prevent late neurologic sequelae in patients with ANS. However, things changed in the HIV era, with frequent reports of symptomatic neurosyphilis in patients who had been adequately treated for early or late latent syphilis [7–10].

The rates of syphilis continue to increase, especially among patients who have or are at risk of acquiring HIV infection [22–24]. The neurologic sequelae of syphilis can be devastating [14]. LPs are invasive, time consuming, and difficult to perform in many settings where patients are diagnosed with syphilis, but they are often necessary. Trying to minimize the number of LPs performed without compromising patient care is helpful, and to this end, selective criteria for performing LP have been advanced. Our data and those of others [13, 25] suggest that application of RPR/CD4 cell count–based criteria improve the ability to identify ANS.

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Potential conflicts of interest. All authors: no conflicts.

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