Cerebrospinal Fluid Abnormalities in Patients with Syphilis: Association with Clinical and Laboratory Features


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**Objective.** To define clinical and laboratory features that identify patients with neurosyphilis.

**Methods.** Subjects (*n* = 326) with syphilis but no previous neurosyphilis who met 1993 Centers for Disease Control and Prevention criteria for lumbar puncture underwent standardized history, neurological examination, venipuncture, and lumbar puncture. Neurosyphilis was defined as a cerebrospinal fluid (CSF) white blood cell count >20 cells/µL or reactive CSF Venereal Disease Research Laboratory (VDRL) test result.

**Results.** Sixty-five subjects (20.1%) had neurosyphilis. Early syphilis increased the odds of neurosyphilis in univariate but not multivariate analyses. In multivariate analyses, serum rapid plasma reagin (RPR) titer increased the odds of neurosyphilis 10.85-fold in human immunodeficiency virus (HIV)–uninfected subjects and 5.98-fold in HIV-infected subjects. A peripheral blood CD4+ T cell count <350 cells/µL conferred a 3.10-fold increased odds of neurosyphilis in HIV-infected subjects. Similar results were obtained when neurosyphilis was more stringently defined as a reactive CSF VDRL test result.

**Conclusion.** Serum RPR titer helps predict the likelihood of neurosyphilis. HIV-induced immune impairment may increase the risk of neurosyphilis.

*Treponema pallidum*, the bacterium that causes syphilis, invades the central nervous system (CNS) early during the course of infection and may elicit meningeal inflammation. The results of studies from the early 1900s [1–5] showed that up to 70% of patients with early-stage syphilis had cerebrospinal fluid (CSF) abnormalities, including pleocytosis, increased protein concentration, and reactive Wasserman test results. *T. pallidum* could be identified by rabbit inoculation test (RIT) in approximately one-fourth of samples, even in the absence of other abnormalities. In patients with later-stage disease, CSF abnormalities and the detection of *T. pallidum* were less common. These results formed the basis of the axiom that *T. pallidum* is cleared from the CSF and CNS in some patients, even without therapy. More recently, Lukehart et al. [6] identified *T. pallidum* in CSF by RIT in 12 (30%) of 40 patients with primary and secondary syphilis and in 0 of 17 patients with early latent or late latent disease. CSF pleocytosis, defined as >5 white blood cells (WBCs)/µL was seen in 16 (40%) of 40 subjects with primary and secondary disease and in 7 (39%) of 18 with latent disease. Similarly, results of the CSF Venereal Disease Research Laboratory (VDRL) test were reactive in 8 (20%) of 40 subjects with primary and secondary syphilis and in 5
pleocytosis, defined as 1 WBCs/μL, was seen in 44 (30%) of 145 CSF samples, and reactive CSF VDRL results were seen in 14 (10%) of 144 CSF samples.

In studies conducted during the preantibiotic era, the presence of conventional CSF abnormalities during any stage of syphilis increased the risk of development of symptomatic neurosyphilis [8]. The relevance of these data to the current treatment era is not known, because modern studies have not assessed the influence of conventional CSF abnormalities on treatment response [6, 7]. Nonetheless, on the basis of clinical experience, the number of individuals with syphilis who develop neurosyphilis after recommended doses of im BPG is believed to be small [9]. For this reason, the Centers for Disease Control and Prevention (CDC) publish guidelines to help identify those individuals with syphilis who are most likely to have neurosyphilis. Lumbar puncture is recommended for these patients, to allow for the rational use of health care resources. Guidelines published in 1993 were revised in 1998 and 2002 [9–11]. All 3 recent guidelines indicate that some experts recommend lumbar puncture for all HIV-infected individuals. This recommendation is based on reports of neurological relapse after appropriate doses of im BPG for early syphilis in HIV-infected individuals, which suggests that the clearance of organisms from the CNS may be impaired by concomitant HIV infection [12–18].

Since July 1996, we have enrolled subjects with syphilis into a study to determine how often CNS T. pallidum infection persists after therapy for neurosyphilis. We report here on an analysis of our baseline data to define the frequency of CSF abnormalities that are consistent with neurosyphilis and the influence of clinical and laboratory measures on the likelihood of such abnormalities.

SUBJECTS AND METHODS

Eligibility criteria and procedures. Subjects were eligible for enrollment if they had syphilis, defined as reactive serum nontreponemal and treponemal serological test results, and met one of the following criteria (based on the 1993 CDC guidelines) [10]: neurological or ophthalmological symptoms or signs during any stage of syphilis, late latent syphilis or syphilis of unknown duration (particularly if the serum nontreponemal antibody titer was ≥1:32), treatment failure, HIV infection (particularly in patients with late latent syphilis), or intent to begin nonpenicillin therapy. Subjects were enrolled at 8 sites: University of Washington, Seattle (132 subjects); Johns Hopkins University, Baltimore (53 subjects); Emory University, Atlanta (41 subjects); Washington University, St. Louis (37 subjects); State University of New York, Brooklyn (23 subjects); Cook County Hospital, Chicago (17 subjects); University of Mississippi, Jackson (15 subjects); and the Chicago Department of Health, Chicago (8 subjects). Subjects were recruited from outpatient sexually transmitted diseases, infectious diseases, ophthalmology, lumbar puncture, and general medical clinics; emergency departments; and in-patient medicine and neurology wards. The study protocol was reviewed and approved by the institutional review boards of each participating site. After written informed consent was obtained, a standardized medical history was obtained, and subjects underwent neurological examination, venipuncture, and lumbar puncture. The syphilis stage was determined according to CDC guidelines; patients with syphilis of unknown duration were included in the group with late latent syphilis [9]. Results of HIV serological tests, plasma HIV-1 RNA copy number, and peripheral blood CD4+ T lymphocyte count were obtained from a review of medical records. Only plasma HIV-1 RNA copy number and peripheral blood CD4+ T lymphocyte count obtained within 90 days of the lumbar puncture (entry date) were used. We used a lower limit of detection for HIV-1 RNA of ≤500 copies/mL, because that was the lower limit of detection when the study began.

Laboratory methods. Serum nontreponemal (VDRL or rapid plasma reagin [RPR]) and treponemal (microhemagglutination–T. pallidum, fluorescent treponemal antibody–absorbed test, T. pallidum particle agglutination or T. pallidum ELISA [Captia Syphilis IgG; Trinity Biotech]) serological tests and CSF glucose, protein, WBC count, red blood cell count, and CSF VDRL tests were performed using standard methods at each of the 8 participating study sites. RPR test titers were determined for all available baseline serum samples in a central laboratory using standard methods, and these values were used in the analysis. In 7 instances, no sample was available for testing in the central laboratory, and the RPR titer obtained by the participating study site was used in the analysis. The presence of T. pallidum in CSF was determined by reverse-transcriptase (RT) PCR, according to published methods [19], with minor modifications. Specifically, the primers were shortened in March 1999 (sense, 5′-CTCTTTTGGACGTAGGTCTT; antisense, 5′-TTACGTGT-TACCGGGCT), and the procedure was optimized for use in a Lightcycler (Roche) in October 2001. For all assays, the limit of detection was 1–10 T. pallidum organisms/mL.

Design and statistical analysis. The analysis in the present
RESULTS

Characteristics of study subjects. The characteristics of the 326 subjects are shown in table 1. Most subjects were men, were infected with HIV, and had late latent syphilis. The median age was 37 years (range, 18–89 years). Two hundred five subjects had received treatment for an episode of nonneurological syphilis before study entry. Of these 205, 49 subjects were treated within 14 days of study entry. As expected, early-stage syphilis was significantly associated with a serum RPR titer $>1:32$ ($P < .001$). Early-stage syphilis was also associated with HIV infection ($P < .001$). Specifically, only 5 (6.0%) of 84 evaluable subjects not infected with HIV had early-stage syphilis, but 93 (44.7%) of 208 evaluable subjects with HIV infection had early syphilis. This disparity was expected, because patients with early-stage syphilis are more likely to have a lumbar puncture if they do not have ocular or neurological symptoms.

Symptoms and signs were categorized into those most consistent with syphilitic meningitis (headache, stiff neck, photophobia, subjective hearing loss, or abnormal finger friction test result in either ear) and with syphilitic ocular disease (subjective decrease in vision, ocular inflammation, or abnormal visual acuity). Eighty-seven subjects (26.7%) met the definition of meningitis alone, 13 (4.0%) met the definition of ocular disease alone, and 25 (7.7%) met the definition for both conditions. The proportion of subjects with ocular disease was significantly greater in the HIV-uninfected group (26.4% vs. 6.0%; $P < .001$), but the proportion of subjects with meningitis was similar between the 2 groups. The greater proportion of HIV-uninfected subjects with ocular disease likely reflects the CDC criteria for lumbar puncture [9–11]—specifically, HIV-uninfected patients are less likely than HIV-infected individuals to undergo lumbar puncture if they do not have ocular or neurological symptoms.

Neurosyphilis in HIV-uninfected subjects. Fifteen HIV-uninfected subjects (16.5%) met our definition of neurosyphilis. Of these 15, 6 subjects had a reactive CSF VDRL test result only, 7 subjects had both a reactive CSF VDRL test result and CSF WBC count $>20$ cells/$\mu$L, and 2 had a CSF WBC count $>20$ cells/$\mu$L only. The median CSF WBC count in HIV-uninfected subjects with neurosyphilis was 29 cells/$\mu$L (range, 0–221 cells/$\mu$L). Neurosyphilis was significantly more likely in subjects with early-stage syphilis (primary, secondary, or early latent disease) and in those with a serum RPR titer $>1:32$ (table 2). In a multivariate logistic regression model, syphilis stage was not significant after controlling for serum RPR titer $>1:32$. Neurosyphilis remained significantly more common in subjects with a serum RPR titer $>1:32$, with an odds ratio (OR) of 10.85 (95% confidence interval [CI], 2.69–43.80) (table 2). Neurosyphilis was not more common in subjects with meningitis or ocular syphilis ($P = .59$ and $P = .75$, respectively).

The above analyses were repeated using reactive CSF VDRL test result as the definition of neurosyphilis, and identical conclusions were obtained. In the univariate analysis, neurosyphilis would be treated as a dependent variable, and the characteristics of the study subjects would be treated as independent variables. The results would be similar to those obtained in the multivariate analysis. If the dependent variable were instead treated as a continuous variable, and the characteristics of the study subjects were treated as independent variables, the results would be different. The dependent variable would be the log of the odds ratio, and the independent variables would be the age, sex, race, and syphilis stage of the study subjects. The results would be similar to those obtained in the univariate analysis.
was significantly more likely in subjects with early-stage syphilis (OR, 10.35; 95% CI, 1.54–69.77; \(P = .02\)) and in those with a serum RPR titer \(\geq 1:32\) (OR, 10.29; 95% CI, 2.77–38.20; \(P < .001\)). Serum RPR titer \(\geq 1:32\) was the only variable that remained significant in the multivariate analysis (OR, 10.28; 95% CI, 2.38–44.40; \(P = .002\)).

**Neurosyphilis in HIV-infected subjects.** Fifty HIV-infected subjects (21.5%) met our definition of neurosyphilis. Of these 50, 16 subjects had a reactive CSF VDRL test result only, 12 subjects had both a reactive CSF VDRL test result and CSF WBC count \(> 20 \text{ cells/ul}\), and 22 had CSF WBC count \(> 20 \text{ cells/ul}\) only. The median CSF WBC count in HIV-infected subjects with neurosyphilis was 29 cells/ul (range, 0–349 cells/ul). Neurosyphilis was significantly more common in subjects with early syphilis, a serum RPR titer \(\geq 1:32\), and a peripheral blood CD4+ T cell count \(\leq 350 \text{ cells/ul}\) or a plasma HIV-1 RNA level \(> 500 \text{ copies/ul}\) (table 3). We reasoned that higher plasma HIV-1 RNA levels might be associated with higher CSF WBC counts because of HIV infection itself [21], rather than infection with *T. pallidum*, and that this could mislead our interpretation of the association between neurosyphilis and plasma HIV-1 RNA level. We did not expect a similar problem with CD4+ T cell count, because HIV-related CSF pleocytosis is less common with lower CD4+ T cell counts [21]. In keeping with our prediction, CSF WBC counts were significantly higher in subjects with plasma HIV-1 RNA levels \(> 500 \text{ copies/ul}\) (\(P < .001\)) but were not higher in subjects with peripheral blood CD4+ T cell counts \(\leq 350 \text{ cells/ul}\) (\(P = .43\)). Thus, in the multivariate analysis shown in table 3, we did not consider plasma HIV-1 RNA levels. After adjusting for syphilis stage and previous treatment for syphilis, neurosyphilis remained significantly more common in HIV-infected subjects who had a serum RPR titer \(\geq 1:32\) (OR, 5.98; 95% CI, 2.43–14.73) or a peripheral blood CD4+ T cell count \(\leq 350 \text{ cells/ul}\) (OR, 3.10; 95% CI, 1.40–6.86) (table 3). Thus, in HIV-infected subjects with both a serum RPR titer \(\geq 1:32\) and a peripheral blood CD4+ T cell count \(\leq 350 \text{ cells/ul}\), neurosyphilis was 18.6 times more likely than in individuals with neither of these features. Neurosyphilis was not more common in subjects with meningitis (\(P = .21\)) but was more common in those with ocular syphilis (\(P = .01\)).

The above analyses were repeated using reactive CSF VDRL test result as the definition of neurosyphilis, with identical conclusions. In the univariate analysis, neurosyphilis was significantly more common in subjects with serum RPR titers \(\geq 1:32\) (OR, 3.57; 95% CI, 1.46–8.78; \(P = .004\)) and in those with peripheral blood CD4+ T cell counts \(\leq 350 \text{ cells/ul}\) (OR, 3.45; 95% CI, 1.32–8.99; \(P = .008\)). In the multivariate analysis, neurosyphilis remained significantly more common in HIV-infected subjects with serum RPR titers \(\geq 1:32\) (OR, 4.09; 95% CI, 1.40–11.96; \(P = .01\)) or peripheral blood CD4+ T cell counts \(\leq 350 \text{ cells/ul}\) (OR, 3.67; 95% CI, 1.33–10.12; \(P = .01\)). Multivariate analysis was repeated for subjects with a nonreactive CSF VDRL test result, in whom CSF WBC \(> 20 \text{ cells/ul}\) would be the only indication of neurosyphilis. Neurosyphilis remained significantly more common in subjects with serum RPR titers \(\geq 1:32\) (OR, 7.25; 95% CI, 1.78–29.47; \(P = .006\)), but neurosyphilis was no longer more common in those with CD4+ T cell counts \(\leq 350 \text{ cells/ul}\). This loss of significance is likely due to the small number of subjects who met the restricted definition of neurosyphilis.

**Identification of T. pallidum in CSF.** *T. pallidum* was identified by RT-PCR in CSF from 26 (8.0%) of 326 subjects (table 4). The identification of *T. pallidum* in CSF was significantly more likely in subjects with early syphilis and in those with a serum RPR titer \(\geq 1:32\), a reactive CSF VDRL test result, or a CSF profile consistent with neurosyphilis. CSF WBC counts were significantly higher in subjects with a positive RT-PCR

<table>
<thead>
<tr>
<th>Table 2. Clinical and laboratory features in 91 HIV-uninfected subjects with and without neurosyphilis.</th>
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<tr>
<td>Features</td>
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<tr>
<td></td>
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<tr>
<td>Stageb</td>
</tr>
<tr>
<td>Early (n = 5)</td>
</tr>
<tr>
<td>Latec (n = 79)</td>
</tr>
<tr>
<td>Serum RPR titer (\geq 1:32) (n = 23)</td>
</tr>
<tr>
<td>Previous syphilis treatment</td>
</tr>
<tr>
<td>0–14 days before entry (n = 54)</td>
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<tr>
<td>15 days–1 year before entry (n = 14)</td>
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<td>&gt;1 year before entry (n = 20)</td>
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</table>

**NOTE.** Neurosyphilis is defined as a cerebrospinal fluid (CSF) white blood cell count \(> 20 \text{ cells/ul}\) or a reactive CSF Venereal Disease Research Laboratory test result. CI, confidence interval; OR, odds ratio; RPR, rapid plasma reagin.

* Adjusted for all features.

b Early-stage syphilis includes primary, secondary, and early latent stages; late-stage syphilis includes late latent syphilis. Data were available for 84 subjects.

c Includes subjects who had syphilis of unknown duration.

**Table 3.** Clinical and Laboratory Features in 91 HIV-Infected Subjects with and without Neurosyphilis.

<table>
<thead>
<tr>
<th>Stageb</th>
<th>Proportion (%)</th>
<th>Unadjusted analysis</th>
<th>Adjusted analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Early (n = 5)</td>
<td>2/69 (2.9)</td>
<td>3/15 (20.0)</td>
<td>8.38 (1.26–55.53)</td>
</tr>
<tr>
<td>Latec (n = 79)</td>
<td>67/69 (97.1)</td>
<td>12/15 (80.0)</td>
<td>Reference</td>
</tr>
<tr>
<td>Serum RPR titer (\geq 1:32) (n = 23)</td>
<td>13/76 (17.1)</td>
<td>10/15 (66.7)</td>
<td>9.69 (2.84–33.11)</td>
</tr>
</tbody>
</table>

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DISCUSSION

The frequent invasion of the CNS by *T. pallidum* has been recognized for decades, and routine examination of the CSF was conducted during the prepenicillin era to guide the duration of heavy-metal therapy. Today, universal lumbar puncture is both impractical and unnecessary. However, continuing uncertainty exists regarding which patients with syphilis should undergo lumbar puncture. For this reason, we sought to identify clinical and laboratory parameters that predict neurosyphilis in both HIV-uninfected and -infected individuals. To our knowledge, our multicenter investigation is the largest modern study to have examined this question. Regardless of stage of syphilis, previous syphilis treatment, and HIV status, neurosyphilis is significantly more common when the serum RPR titer is ≥1:32. HIV-infected individuals with both serum RPR titers ≥1:32 and peripheral blood CD4+ T cell counts ≤350 cells/μL are at an even higher risk of neurosyphilis. We did not find an association between meningitis and our laboratory-based definition of neurosyphilis in all subjects nor between ocular syphilis and our definition of neurosyphilis in HIV-uninfected subjects. These unexpected findings likely reflect imprecision inherent in the clinical definitions. Both were based on symptoms or a simple bedside test. The inclusion of specific otological or ophthalmological findings would likely have increased the diagnostic accuracy.

How can our findings be best used to guide clinicians in the selection of patients with syphilis who are most likely to benefit from CSF examination? On the one hand, all individuals with high (≥1:32) serum RPR titers or low (≤350 cells/μL) peripheral blood CD4+ T cell counts could be examined by lumbar puncture at the time of their diagnosis of syphilis. Those with CSF abnormalities would then be treated with a regimen recommended for neurosyphilis [9], to prevent progression to symptomatic or more severe disease. This approach would be the most comprehensive but would result in treatment of some patients who might ultimately be able to control their CNS infections without neurosyphilis therapy. However, because it is not possible to predict in which patients CSF infections will or will not resolve, it can be argued that this approach is the safest.

On the other hand, an alternative approach would be to...
Table 4. Clinical and laboratory features of 326 subjects with and without identification of *Treponema pallidum* in cerebrospinal fluid (CSF) by reverse-transcription polymerase chain reaction (RT-PCR).

<table>
<thead>
<tr>
<th>Feature</th>
<th>RT-PCR result, proportion (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>215/300 (71.7)</td>
<td>20/26 (76.9)</td>
</tr>
<tr>
<td>Stage</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>5/268 (1.9)</td>
<td>0/24 (0.0)</td>
</tr>
<tr>
<td>Secondary</td>
<td>48/268 (17.9)</td>
<td>11/24 (45.8)</td>
</tr>
<tr>
<td>Early latent</td>
<td>31/268 (11.6)</td>
<td>3/24 (12.5)</td>
</tr>
<tr>
<td>Late latent(^b)</td>
<td>184/268 (68.7)</td>
<td>10/24 (41.7)</td>
</tr>
<tr>
<td>Serum RPR titer (\geq1:32)</td>
<td>113/300 (37.7)</td>
<td>25/26 (96.2)</td>
</tr>
<tr>
<td>Reactive CSF VDRL test result</td>
<td>28/299 (9.4)</td>
<td>13/26 (50.0)</td>
</tr>
<tr>
<td>Neurosyphilis,(^c)</td>
<td>49/298 (16.4)</td>
<td>16/26 (61.5)</td>
</tr>
<tr>
<td>Previous syphilis treatment</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>0–14 days before entry</td>
<td>153/300 (51.0)</td>
<td>17/26 (65.4)</td>
</tr>
<tr>
<td>15 days–1 year before entry</td>
<td>61/300 (20.3)</td>
<td>5/26 (19.2)</td>
</tr>
<tr>
<td>&gt;1 year before entry</td>
<td>86/300 (28.7)</td>
<td>4/26 (15.4)</td>
</tr>
</tbody>
</table>

**NOTE.** CSF, cerebrospinal fluid; RPR, rapid plasma reagin; RT-PCR, reverse-transcription polymerase chain reaction; VDRL, Venereal Disease Research Laboratory.

\(^a\) For the comparison between early-stage (primary, secondary, and early latent) and late latent disease. Data were available for 292 subjects.

\(^b\) Includes subjects with syphilis of unknown duration.

\(^c\) Neurosyphilis is defined as a CSF white blood cell count \(\geq20\) cells/\(\mu\)L or a reactive CSF VDRL test result.

postpone CSF evaluation for 6–12 months after conventional syphilis treatment and then to use the same criteria to select those individuals who are at the highest risk for neurosyphilis. Such an approach would likely result in fewer lumbar punctures and thus decrease costs because of the decline in serum RPR titers after conventional syphilis therapy. The number of patients put at risk by the latter approach because of loss to follow-up, combined with the subsequent development of symptomatic or more severe neurosyphilis, is not known. This risk may be greatest in those with concomitant HIV infection, in whom early neurorelapse after treatment with im BPG may be more likely [12, 18]. This issue is particularly relevant at present, because the rates of syphilis in men who have sex with men, a group with a high risk of HIV infection, in the United States and Europe are dramatically increasing [22–26].

Regardless of the approach, routine laboratory CSF tests will fail to identify some patients with CNS invasion. In our study, *T. pallidum* was identified in 10 CSF samples that were otherwise normal, which likely reflects very recent CNS invasion [27]. The clinical implications of such a finding have been debated; experts recommend the consideration of treatment for neurosyphilis in HIV-infected but not in HIV-uninfected individuals in whom *T. pallidum* is identified in otherwise normal CSF [28] because of concern about HIV-associated impaired clearance of CNS *T. pallidum*. Consistent with the results of previous studies, we found no association between the identification of *T. pallidum* in CSF by RT-PCR and HIV status [6, 7]. The significant association that we observed between a peripheral blood CD4\(^+\) T cell count \(\leq350\) cells/\(\mu\)L and neurosyphilis argues that, once invasion has occurred, the persistence of CNS infection with the development of CSF pleocytosis and reactive CSF VDRL test result may be more likely in those with HIV-mediated immunosuppression.

The limitations of our study should be acknowledged. Our results are applicable to individuals who met the criteria that we specified for lumbar puncture and who did not have a prior episode of neurosyphilis. We did not collect information on antiretroviral therapy in the HIV-infected subjects. Instead, we focused on peripheral blood CD4\(^+\) T cell counts and plasma HIV-1 RNA concentrations, which are markers of the efficacy of therapy. Because of the demographics of syphilis in the United States and the criteria that we used for lumbar puncture, most of our subjects were HIV infected. Nonetheless, our study population included lumbar puncture data on 91 HIV-uninfected subjects. This number is quite similar to the number of HIV-uninfected subjects in a recent and well-regarded syphilis study that also included CSF examination [7]. It could also be argued that our laboratory criteria for neurosyphilis include individuals with CSF pleocytosis caused by HIV rather than by *T. pallidum* infection. We think that this is unlikely to be the
case. Twenty-eight of 50 HIV-infected subjects who met our criteria for neurosyphilis also had a reactive CSF VDRL test result, which would not be expected solely on the basis of HIV infection. Furthermore, our cutoff for defining abnormal CSF WBC counts is above the mild pleocytosis caused by HIV itself [20]. When we more stringently defined neurosyphilis as a reactive CSF VDRL test result, thus removing diagnostic uncertainty due to concomitant HIV infection, the associations between neurosyphilis and serum RPR titer or peripheral blood CD4 cell count remained significant.

We demonstrate that a serum RPR titer $\geq 1:32$ is predictive of neurosyphilis in all individuals with syphilis and that a peripheral blood CD4 $^+$ T cell count $\geq 350$ cells/$\mu$L is an additional risk factor for neurosyphilis in HIV-infected individuals. The risk associated with these parameters is independent of previous syphilis therapy and stage of syphilis. Because of the increased risk of neurorelapse after treatment with im BPG in HIV-infected individuals, we recommend that immediate lumbar puncture be performed in HIV-infected patients with syphilis, regardless of syphilis stage, particularly when the serum RPR titer is $\geq 1:32$ or the peripheral blood CD4 $^+$ T cell count is $\geq 350$ cells/$\mu$L. It is more difficult to judge when to perform lumbar puncture in HIV-uninfected patients with syphilis, because CSF abnormalities in the setting of early syphilis may or may not resolve spontaneously after treatment with im BPG. However, the 10.28-fold increased risk of a reactive CSF VDRL test result in HIV-uninfected subjects with a serum RPR titer $\geq 1:32$, regardless of syphilis stage and previous syphilis treatment, suggests that it is also reasonable to perform immediate lumbar puncture in such individuals. Further study to define factors that predict resolution of CSF abnormalities in early syphilis is needed.

Acknowledgments

We thank Arturo Centurion, Department of Medicine (Infectious Diseases), University of Washington, Seattle, for helpful advice and discussions, and Rolf Pederson, Seattle-King County Department of Public Health, Seattle; Lauren Tantalo, Sopheap Chhay, Trudy Jones, and Joseph R. Zunt, Department of Neurology, University of Washington; and Chellynn Hinds, State University of New York–Downstate, Brooklyn, for technical assistance.

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