Syphilis Detection in Cerebrovascular Disease

Roger E. Kelley, MD, Lynda Bell, RN, Susan E. Kelley, RN, and Shih-Chang Lee, PhD

To determine the importance of syphilis testing in cerebrovascular disease, we prospectively assessed 218 consecutive patients with either transient ischemic attack or completed stroke. The results from this study group were compared with those from a control group of 150 neurological patients without cerebrovascular disease. Of 275 patients from both groups specifically tested by the fluorescent treponemal antibody-absorption test, 34% of the study group were seropositive compared with 18% of the controls ($\chi^2 = 7.7, p < 0.01$). Fifty-four percent of the patients with a positive fluorescent treponemal antibody-absorption test underwent a cerebrospinal fluid examination; meningovascular syphilis was detected in one (0.4%) of these. This patient was a homosexual male with antibodies to the human immunodeficiency virus; a second patient, with possible meningovascular syphilis, also had antibodies to this virus. Despite the relatively high rate of syphilis seropositivity noted in our study group, syphilis was not found to be a common cause of cerebrovascular disease; therefore, routine screening is seen to be of low diagnostic yield. Attention to patients who are at higher risk for syphilitic infection, patients with clinical features suggestive of meningovascular syphilis, and the proper choice of serologic studies can help make the assessment of syphilis seropositivity more clinically appropriate and cost effective. (Stroke 1989;20:230–234)
bolism (57%), lacune (15%), primary intracerebral hemorrhage (10%), subarachnoid hemorrhage (6%), TIA (12%), and cerebral venous thrombosis (0.5%). CT brain scans were obtained in all but one patient. The difference in the rate of seropositivity between the CVD and control patients was assessed with a chi-squared test with Yates' correction. 1

Results

The results of RPR, serum FTA-ABS, and CSF VDRL testing in the CVD and control patients are also presented in Table 1. The RPR seropositivity rate was lower than that of the FTA-ABS in both groups. Of the 142 CVD patients who had both RPR and FTA-ABS testing, 14 (10%) were positive by the RPR and FTA-ABS, and 23 (33%) were positive by the FTA-ABS. There was one patient with a positive RPR and a negative FTA-ABS, and this was presumably a false-positive result related to presence of the lupus anticoagulant.

Of the 218 CVD patients, 87 were blacks; 60 (69%) were tested by the FTA-ABS, and 26 (43%) were positive. Of the 96 Hispanics, 70 (73%) were tested by the FTA-ABS, and 23 (33%) were positive. The relation of FTA-ABS seropositivity to race, age, and sex is summarized in Table 2. (Our CVD group also included two Oriental patients not included in Table 2.) In addition to a difference in the seropositivity rate among the three major races, there was a tendency for the rate to be lower in females than in males (29% versus 39% for those tested). These findings might well have reflected the referral pattern of our hospital, however. We did not find a correlation between syphilis seropositivity and age, nor was a correlation found with stroke type.

For all 368 patients, the CVD group had a seropositivity rate of 24% compared with 15% for the controls ($\chi^2=3.9, p<0.05$). For only those patients who had FTA-ABS testing, the rate of seropositivity was 34% for the CVD patients and 18% for the controls ($\chi^2=7.7, p<0.01$). The mean age was 57.0 years for the CVD patients and 50.2 years for the controls. The control group comprised 30% blacks (41% male, 59% female), 33% Hispanics (54% male, 46% female), and 37% non-Hispanic Caucasians (54% male, 46% female).

Of 152 CVD patients tested by the FTA-ABS, 48 (32%) had a CSF examination including the VDRL; 28 of the 52 CVD patients with a positive FTA-ABS (54%) had a CSF examination. The major reason that a CSF examination was not obtained in other patients with positive serologies included the following: mass effect by CT brain scan, moribund

Table 1. Tests Performed to Screen for Syphilis in Cerebrovascular Disease Patients and Controls

<table>
<thead>
<tr>
<th>Test</th>
<th>CVD patients (N=218)</th>
<th>Control patients (N=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tested (no. %)</td>
<td>Positive (no. %)</td>
</tr>
<tr>
<td>RPR</td>
<td>154 (71)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>152 (70)</td>
<td>52 (34)</td>
</tr>
<tr>
<td>CSF VDRL</td>
<td>60 (28)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>One or more of the above tests</td>
<td>177 (81)</td>
<td>—</td>
</tr>
</tbody>
</table>

CVD, cerebrovascular disease; RPR, rapid plasma reagin; FTA-ABS, serum fluorescent treponemal antibody-absorption; CSF VDRL, cerebrospinal fluid Venereal Disease Research Laboratory.

Table 2. Serum FTA-ABS Results in Cerebrovascular Disease Study Group Subgroups

<table>
<thead>
<tr>
<th>Age range (yr)</th>
<th>Black Males (n=37)</th>
<th>Black Females (n=50)</th>
<th>Hispanic Males (n=53)</th>
<th>Hispanic Females (n=43)</th>
<th>Non-Hispanic Caucasian Males (n=14)</th>
<th>Non-Hispanic Caucasian Females (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
<td>ND</td>
<td>Pos</td>
<td>Neg</td>
<td>ND</td>
</tr>
<tr>
<td>10-29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>50-59</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>60-69</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>70-79</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>80-91</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>14</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>% of N</td>
<td>32</td>
<td>41</td>
<td>27</td>
<td>28</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>% of those tested</td>
<td>44</td>
<td>56</td>
<td>—</td>
<td>42</td>
<td>58</td>
<td>—</td>
</tr>
</tbody>
</table>

FTA-ABS, serum fluorescent treponemal antibody-absorption test; Pos, positive; Neg, negative; ND, not performed.
condition, anticoagulant therapy, previous treatment for positive serology, refusal of the procedure, and unsuccessful attempt at lumbar puncture.

The CSF examination revealed either no cells or a mild lymphocytic pleocytosis, normal or mildly elevated CSF protein concentration, no significant increase in CSF immunoglobulin G (IgG) concentration by protein electrophoresis, and a nonreactive CSF VDRL except in two instances. One patient, a 59-year-old Hispanic man, presented with dysarthria and a mild right hemiparesis. CT brain scan revealed multiple small (lacunar-type) subcortical infarcts on the left. Two infarcts, in the left internal capsule and the lentiform nucleus, enhanced with contrast. A cerebral arteriogram revealed minor plaque formation at the origin of the left anterior cerebral artery with focal narrowing of the proximal left anterior cerebral artery and the left pericallosal artery (Figure 1). The RPR was positive at 1:256 dilution and the FTA-ABS was 3+. The CSF was clear and colorless with 112 erythrocytes (100% mononuclear)/mm$^3$, a glucose concentration of 49 mg%, a protein concentration of 112 mg%, and a reactive VDRL. CSF protein electrophoresis revealed the CSF IgG concentration to be 27.1 mg% (normal, 0.7–6.1 mg%) and an elevated CSF/serum IgG ratio of 1.76 (normal, <0.77). He was treated with a 14-day course of intravenous penicillin for meningovascular syphilis. Of note, he was homosexual, with the presence of antibodies to the human immunodeficiency virus (HIV) and a normal absolute number of helper T cells (638/mm$^3$) but a T4/T8 ratio of 0.5 (normal, 1.1–3.5). The patient was lost to follow-up, and repeat CSF results were not available.

The second patient, a 46-year-old black homosexual man, presented with a vertebrobasilar TIA and had suffered a well-documented right subcortical (lacunar-type) infarction 6 months previously. He had had hypertension since age 16. He was HIV antibody-positive, with a T4/T8 ratio of 0.2 and a low absolute number of helper T cells (144/mm$^3$). His serum RPR was positive at 1:8 dilution, and his serum FTA-ABS was 2+. His CSF was clear and colorless with 2 leukocytes (100% mononuclear)/mm$^3$, a glucose concentration of 51 mg%, a protein concentration of 99 mg%, a CSF IgG concentration of 35 mg%, a CSF/serum IgG ratio of 0.74, and a negative VDRL. He had received a 3-week course of intramuscular benzathine penicillin G (2.4 million units/week) within the past 6 months, but in light of his elevated CSF IgG concentration, he was treated as a patient with possible meningovascular syphilis with a 10-day course of intravenous penicillin. Neither patient had pupillary involvement compatible with advanced syphilis. All other patients in our series who were found to have positive syphilis serology that was believed not to have been adequately treated in the past received a standard course of therapy for latent syphilis.
No control patient was diagnosed as having neurosyphilis. One control patient was HIV antibody-positive and had the acquired immunodeficiency syndrome (AIDS).

Discussion

There are a number of serologic tests presently available for the detection of syphilitic infection. The nontreponemal tests, which include the VDRL and RPR, measure an antibody termed "reagin" that is a nonspecific immunoglobulin found in both treponemal and nontreponemal diseases. CSF VDRL remains the most specific indicator of neurosyphilis, but the sensitivity is uncertain. Treponemal antibody tests are more specific than nontreponemal tests as they detect antibodies usually related directly to treponemal infections. The two most commonly used are the serum FTA-ABS test and the microhemagglutination assay for T. pallidum antibodies (MHA-TP).

After a 5-year trend of declining incidence of primary and secondary syphilis, there has recently been reported an increase. Although this was previously attributed to an increasing incidence among homosexual males, more recent studies report an increase largely among heterosexuals, not confined to males. Our study demonstrates the not infrequent finding of positive syphilis serology in patients hospitalized with stroke and TIA. Seropositivity raises the possibility of meningovascular syphilis, but we found only one CVD patient (0.4%) with definite disease and a second patient with possible disease.

Of patients specifically tested by the FTA-ABS, 34% were seropositive. This relatively high rate presumably reflects the referral pattern of our hospital and cannot necessarily be extrapolated to the general population. The RPR was reactive in only 28% of the patients with a positive FTA-ABS in whom both tests were performed. The lower sensitivity of the RPR indicates that it is not a reliable test to screen for advanced syphilis as has been emphasized in recent reports on neurosyphilis.

Control patients specifically tested with the FTA-ABS had a FTA-ABS seropositivity rate of 18%. The fact that only one person with definite meningovascular syphilis was detected among our 218 CVD patients suggests that other differences between the CVD and control groups, such as the lower percent of non-Hispanic Caucasians in the CVD group (15%) compared with the control group (33%), may be responsible for the disproportionately higher rate of seropositivity in CVD patients.

A recent study of CSF VDRL results reported that only three of 2,536 tests performed at one hospital in 1980 were reactive. Other CSF findings of importance in the detection of neurosyphilis include elevated leukocyte count, increase in the total protein concentration, and an elevation of the IgG titer. Although the percentage of all 218 CVD patients with a positive FTA-ABS approached one in four, only 54% of these patients had a CSF examination. It is possible, therefore, that our detection rate of meningovascular syphilis was falsely low. In addition, the indolent course that is believed to be typical of present-day meningovascular syphilis may prevent such patients from being detected in a study of acute CVD.

Routine screening of stroke and TIA patients for meningovascular syphilis has a low diagnostic yield. Selective testing with a treponemal antibody test is indicated in patients without apparent risk factors for stroke, patients who are at high risk for seropositivity, and patients who have an indolent or atypical course. Not only does meningovascular syphilis remain a concern as a treatable etiology of stroke, but in addition, only 33% of our patients with a reactive FTA-ABS had a history of positive syphilis serology that had been adequately treated. Patients who have a reactive FTA-ABS (or other treponemal antibody test) should undergo a CSF examination if the lumbar puncture can be performed safely.

Perhaps of special importance are patients at risk for AIDS in light of the relatively high attack rate of syphilis in homosexual men, the correlation between syphilis exposure and HIV infection in homosexual men, and the impaired resistance to infection in AIDS. There have been recent reports of two homosexual men, one with documented HIV infection, who developed neurosyphilis despite prior adequate treatment for secondary syphilis. The one patient in our CVD group with confirmed meningovascular syphilis was a homosexual male with antibodies to HIV; a second patient, also HIV-positive, had possible meningovascular syphilis. In addition, four patients with neurosyphilis in association with HIV have recently been reported, and this has led to speculation that HIV infection may modify syphilis infection. This hypothesis was not supported by a recent autopsy study of meningoencephalitis, however.

In summary, the prevalence of seropositivity in our series underscores the continued need to consider meningovascular syphilis in the differential diagnosis of CVD. Our low detection rate despite the high rate of seropositivity, however, suggests that a seropositive stroke patient does not necessarily have to be treated for meningovascular syphilis if a lumbar puncture cannot be performed unless clinical features strongly support this possibility.

References


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