Cerebrospinal Fluid IgG and IgM Indexes as Indicators of Active Neurosyphilis

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Serological and non-serological tests were performed in matched samples of cerebrospinal fluid and serum from 236 syphilitic patients. An increased IgG or IgM Index, or both, was found about 70 times more often in symptomatic neurosyphilis than in latent syphilis without involvement of the central nervous system. An increased Ig index, together with a cell count >5/μL, was only found in symptomatic neurosyphilis. Although the numbers of data are small, we conclude that the IgG and IgM indexes are valuable tests in the diagnosis of syphilitic involvement of the central nervous system.

Additional Keyphrases: likelihood ratio · predictive value

According to the World Health Organization (WHO) (1) the traditional criteria for involvement of the central nervous system (CNS) in syphilis are: a positive VDRL (Venereal Diseases Research Laboratory) test, pleocytosis, and an increased concentration of protein in cerebrospinal fluid (CSF). The VDRL test is not a reliable indicator because it gives a negative test result in 30% to 57% of the patients with active neurosyphilis (1). Pleocytosis and increased protein are signs of inflammation, and are not specific for syphilitic involvement of the CNS (1).

The present study was performed to evaluate some CSF tests as indicators for syphilitic CNS involvement. We estimated test characteristics (true-positive rate, true-negative rate), likelihood ratios of positive test results, and predictive values.

Materials and Methods

Subjects

Matched CSF and serum samples were obtained from 236 syphilitic patients. All samples were screened for antibodies to human immunodeficiency virus (HIV); positive samples were discarded from the study (n = 11). Samples were also excluded if nonvenereal treponematosis (n = 3), intravenous penicillin treatment (n = 10), or other (neurologic) diseases (n = 6) were suspected.

CSF samples containing more than 150 erythrocytes per microliter were not used (n = 3).

We studied two groups of patients:

- Those with latent syphilis without CNS involvement (n = 75), i.e., patients with asymptomatic seroreactive syphilis in which CSF treponemal reactivity is negative (1). Latent syphilis means no clinical evidence of active syphilis of any system.
- Those with symptomatic neurosyphilis (n = 13), denoted by the development of neurological signs and (or) symptoms of syphilitic meningovasculitis and (or) parenchymatous neurosyphilis in patients with latent syphilis.

The first group comprised 23 women (ages 21–84 years, mean 37, median 33) and 52 men (ages 20–69 years, mean 36, median 35). The second group comprised three women (ages 57–79 years, mean and median 68) and 10 men (ages 38–82 years, mean and median 56), who displayed the following neurosyphilitic syndromes: cerebral syphilitic meningitis (n = 3), cerebral syphilitic vasculitis (n = 4), tabes dorsalis (n = 1), dementia paralytica (n = 2), and taboparalysis (n = 3).

The remaining 115 patients (not studied here) were patients with positive treponemal reactivity in their CSF.

Procedures

Serological tests: All CSF and serum samples were investigated with the VDRL test, the FTA-ABS (fluorescent treponemal antibody absorption) test, the I9S(IgM)-FTA-ABS test, and the TPHA (Treponema pallidum hemagglutination assay; Japan Lyophilization Company). The CSF-TPHA results were considered positive if samples were reactive at a fourfold dilution. For the FTA-ABS and the I9S (IgM)-FTA-ABS tests, we used CSF samples diluted fivefold in phosphate-buffered isotonic saline (pH 7.2, containing phosphate, 10 mmol/L, and NaCl, 150 mmol/L). In addition, we investigated serum samples with the TPI (T. pallidum immobilization) test.

Nonserological tests: We performed CSF cell counts in triplicate in a Fuchs–Rosenthal counting chamber. The protein content was estimated with a Coomassie Brilliant Blue method (Microprotein Rapid Skat Diagnostic Kit; Lancer, Kildare, Ireland) (2). Albumin and IgG in CSF and serum were quantitatively determined turbidimetrically (3); IgM was quantified by fluoroimmunoassay (4). The albumin mass ratio—albumin in CSF (× 10³)/albumin in serum—was used as a test for the integrity of the blood–brain barrier (5). IgG and IgM indexes were calculated from CSF/serum ratios of IgG or IgM and albumin concentrations, by the following formulas:

\[
\text{IgG index} = \frac{[\text{IgG}]_{\text{CSF}}}{[\text{IgG}]_{\text{serum}}} \frac{[\text{albumin}]_{\text{CSF}}}{[\text{albumin}]_{\text{serum}}}
\]

\[
\text{IgM index} = \frac{[\text{IgM}]_{\text{CSF}}}{[\text{IgM}]_{\text{serum}}} \frac{[\text{albumin}]_{\text{CSF}}}{[\text{albumin}]_{\text{serum}}}
\]

An increased Ig index presumably indicates intrathecal synthesis of the corresponding immunoglobulin. Oligoclonal

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immunoglobulins in CSF were demonstrated by electrophoresis on cellulose acetate (6).

The upper limits of normal (97.5 percentile) for the protein content and albumin ratio were, respectively: 0.50 g/L and 7.8. For the cell counts and for the IgG and IgM indexes, we used discrimination values that exceeded the accepted upper limits of normal, favoring specificity at the cost of sensitivity. We used the following cutoff values (upper limits of normal are given in parentheses): mononuclear cells: 5 per μL (3 per μL); IgG index: 0.70 (0.62); IgM index: 0.10 (0.07).

Statistics: True-positive rate (TPR) = sensitivity = the proportion of patients with symptomatic neurosyphilis who have a positive test result. True-negative rate (TNR) = specificity = the proportion of patients with latent syphilis without CNS involvement who have a negative test result. Likelihood ratio (LR) of a positive test result = TPR/(1 – TNR).

We calculated the predictive value of a positive test result (PV+) according to Bayes' theorem:

\[
P(V^+) = \frac{P(P + (1 - P)/LR]}
\]

where \(P\) = pretest probability of CNS involvement.

Exact 95% confidence limits for each test characteristic were taken from scientific tables (7). To assess the significance of proportion differences between subgroups, we used the chi-square test for small samples (8).

The 95% confidence limits of likelihood ratios were estimated by computer program (9).

Results

Table 1 shows the number of positive test results found in patients with neurosyphilis and in syphilitic patients without CNS involvement. Within both groups there was no significant difference between males and females. Influence of age on the test results is to be expected only for the albumin ratio and total protein content (10). Within the group of patients with neurosyphilis, albumin ratio and protein concentration was so marked that the influence of age could be neglected. The estimated test characteristics (TPR, TNR, and LR of positive test results) are given, with their 95% confidence limits. For each test the difference between the two groups of syphilitic patients was highly significant (\(P < 0.001\)). Moreover, all likelihood ratios were significantly (\(P < 0.05\)) greater than 1, being not included within the 95% confidence intervals.

Table 2 summarizes the predictive values for a number of pretest probabilities of CNS involvement.

Discussion

The traditional CSF tests to diagnose neurosyphilis are the VDRL test, the cell count, and protein content. The VDRL test is very specific but not sensitive. Increases in cell count and protein content are not specific for syphilitic inflammation of the CNS (1). We performed the present study to evaluate some other CSF tests as indicators for syphilitic involvement of the CNS. Therefore we studied two groups of patients with syphilis: one group with symptomatic neurosyphilis, the other group with latent syphilis, in which CNS involvement could most probably be excluded.

Table 2. Predictive Values Given a Likelihood Ratio and Pretest Probability of CNS Involvement in Patients with Positive CSF Serology

<table>
<thead>
<tr>
<th>Predictive value, %, for pretest probability (%) of</th>
<th>LR</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrophoresis oligoclonal Ig</td>
<td>3.8</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Albumin ratio ≥7.9</td>
<td>5.8</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Cell count ≥5/μL</td>
<td>7.4</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Total protein ≥0.51 g/L</td>
<td>8.7</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>Cell count ≥10/μL</td>
<td>20.2</td>
<td>17</td>
<td>52</td>
</tr>
<tr>
<td>IgM index ≥0.10</td>
<td>57.7</td>
<td>37</td>
<td>75</td>
</tr>
<tr>
<td>IgG index ≥0.70</td>
<td>63.5</td>
<td>39</td>
<td>77</td>
</tr>
<tr>
<td>IgG index ≥0.70 and (or) IgM index ≥0.10</td>
<td>68.2</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Cell count ≥5/μL and IgG index ≥0.70</td>
<td>∞</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>and (or) IgM index ≥0.10</td>
<td>∞</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
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because of negative treponemal CSF serology (1). As Table 1 shows, electrophoresis of CSF proteins yielded little information, with 16% of the syphilitic patients without CNS involvement showing oligoclonal Ig bands. The true-negative rate of this test was low (64%), and the true-positive rate was even lower (62%); thus the LR for a positive test result was 3.8. The albumin ratio will not give more information than the protein content. Using a higher discrimination value of 10 cells per μL increased the estimated LR from 7.4 to 20.2. An increased IgG or IgM index was found about 70 times more often in asymptomatic neurosyphilis than in latent syphilis without CNS involvement.

Although the likelihood ratios were estimated from a small data sample, we conclude that the traditional indicators for inflammation of CNS—a cell count of >5/μL and an increased protein content—change a pretest probability of CNS involvement from 5% into about 30% (Table 2).

In contrast, a cell count of >10/μL gives a predictive value of about 50%, and an increased Ig index can change the pretest probability of 5% to 75%.

Because no one in the group of syphilitic patients without CNS involvement had an increased IgG or IgM index accompanied by a pleocytosis of more than 5 cells per microliter, the combination of positive results for these tests will give a very high likelihood ratio (LR = ∞, see Table 1). Thus in the case of positive treponemal CSF serology, when other neurological conditions are improbable, such a finding is very suggestive for syphilitic CNS involvement even if the pretest probability is low. Such is the case in asymptomatic neurosyphilis. Low values, however, do not rule out this condition.

In conclusion: although our reported ranges of the 95% confidence limits of the estimated test characteristics are rather widespread, owing to small sample sizes, the IgG and IgM indexes are valuable tests in the diagnosis of syphilitic CNS involvement.

We thank Drs. J. van Manen, G. A. J. de Koning, D. Tio, T. M. Starink, and L. J. Emsbroek for their helpful cooperation and Mrs. G. Lagerveld for her assistance at the outpatients department.

References
1. Treponemal infections. WHO Tech Rep Ser 1982;674:34.