Cerebrospinal fluid immunoglobulins in neurosyphilis*

F G SCHNAIT, B L SCHMIDT, AND A LUGER
From the Department of Dermatology, Hospital Vienna-Lainz and the Ludwig-Boltzmann Institute for Dermatovenerological Serodiagnosis, Vienna, Austria

SUMMARY Using the fluorescent treponemal antibody-absorption (FTA-ABS) test and the solid phase haemadsorption assay (SPHA) Treponema pallidum-specific IgA was found in the cerebrospinal fluid (CSF) of patients with neurosyphilis but not in those with late latent syphilis. The presence of T pallidum-specific IgA in the CSF may inhibit the antitreponemal activity of IgG and thus play some part in the pathogenesis of neurosyphilis.

Introduction
The occurrence of Treponema pallidum-specific immunoglobulins has been studied extensively during recent years and serological methods for the diagnosis of syphilis have become both specific and easy to perform. Since the development of the solid phase haemadsorption assay (SPHA) for the routine demonstration of T pallidum-specific 19S-IgM, even syphilitic reinfection can be easily diagnosed serologically and treatment failures can be detected.

Little is known about the presence and quantitative distribution of T pallidum-specific immunoglobulins in the cerebrospinal fluid (CSF) of patients with neurosyphilis. The present study was performed to investigate these specific immunoglobulins (Ig) A and G in the CSF of patients with neurosyphilis and of those with late latent syphilis without involvement of the central nervous system (CNS).

Patients and methods
NEUROSYPHILIS
Six patients (four men and two women), aged 53-79 years, had signs or symptoms of neurosyphilis or both (table I). All had high titres in the T pallidum haemagglutination assay (TPHA-CSF) ranging from 2560-40 960. The TPHA indices* were above 100, thus strongly suggesting neurosyphilis (unpublished data).

LATE LATENT SYPHILIS
Six patients (three men and three women) aged 49-79 years with late latent syphilis but no CNS involvement were investigated (table II). The CSF-TPHA titres were low (ranging from 40-640) and the TPHA indices were all below 100.

SEROLOGICAL TECHNIQUES
The presence of T pallidum-specific IgG and IgA was determined both by the FTA-ABS test (using FITC-conjugated heavy-chain monospecific antisera, DAKO, diluted 1/30 for IgA and 1/200 for IgG) and by the SPHA with the same reagents.1

Results
T PALLIDUM-SPECIFIC IMMUNOGLOBULINS
IgG
T pallidum-specific IgG was present in the serum and the CSF of all the patients studied. There were no significant differences in the quantitative distribution between the group of patients with neurosyphilis and those without CNS involvement (table III).

IgA
T pallidum-specific IgA was detected by the SPHA in the serum of all the patients with neurosyphilis (mean

*TPHA index = \( \frac{\text{CSF-TPHA titre}}{\text{albumin quotient}} \)

(albumin quotient = \( \frac{\text{CSF albumin (mg/dl)} \times 10^3}{\text{Serum albumin (mg/dl)}} \))
Cerebrospinal fluid immunoglobulins in neurosyphilis

TABLE I Results of serological tests in serum and cerebrospinal fluid of patients with neurosyphilis

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Clinical diagnosis</th>
<th>Serum VDRL titre</th>
<th>TPHA titre</th>
<th>FTA-ABS (mg/100ml)</th>
<th>Cerebrospinal fluid VDRL titre</th>
<th>TPHA titre</th>
<th>FTA-ABS (mg/100ml)</th>
<th>Albumin (mg/100ml)</th>
<th>Cells (x 10^6/l)</th>
<th>Albumin (mg/100ml)</th>
<th>TPHA index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Meningovascular syphilis</td>
<td>1/2</td>
<td>1/10 240</td>
<td>+ +</td>
<td>1/2</td>
<td>1/10 240</td>
<td>+ +</td>
<td>2</td>
<td>28</td>
<td>1530</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Taboparesis</td>
<td>1/2</td>
<td>1/20 480</td>
<td>+ ++</td>
<td>1/2</td>
<td>1/10 240</td>
<td>+ +</td>
<td>2</td>
<td>28</td>
<td>1700</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>General paresis</td>
<td>1/4</td>
<td>1/20 480</td>
<td>+ +</td>
<td>1/1</td>
<td>1/2 560</td>
<td>+ +</td>
<td>52</td>
<td>68</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>General paresis</td>
<td>1/16</td>
<td>1/20 480</td>
<td>+ +</td>
<td>1/1</td>
<td>1/2 560</td>
<td>+ +</td>
<td>3</td>
<td>140</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Taboparesis</td>
<td>1/1</td>
<td>1/5120</td>
<td>+ +</td>
<td>1/1</td>
<td>1/2 560</td>
<td>+ +</td>
<td>3</td>
<td>63</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Taboparesis</td>
<td>1/16</td>
<td>1/81 920</td>
<td>+ +</td>
<td>1/1</td>
<td>1/40 960</td>
<td>+ +</td>
<td>2</td>
<td>12</td>
<td>8200</td>
<td></td>
</tr>
</tbody>
</table>

+ + and + ++ = positive

TABLE II Results of serological tests in serum and cerebrospinal fluid of patients with late latent disease but without symptoms of neurosyphilis

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Serum VDRL titre</th>
<th>TPHA titre</th>
<th>FTA-ABS (mg/100ml)</th>
<th>Cerebrospinal fluid VDRL titre</th>
<th>TPHA titre</th>
<th>FTA-ABS (mg/100ml)</th>
<th>Albumin (mg/100ml)</th>
<th>Cells (x 10^6/l)</th>
<th>Albumin (mg/100ml)</th>
<th>TPHA index</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>1/32</td>
<td>1/20 480</td>
<td>+ +</td>
<td>1/16</td>
<td>+ +</td>
<td>0.3</td>
<td>17</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1/1</td>
<td>1/160</td>
<td>+ +</td>
<td>1/40</td>
<td>+ +</td>
<td>0.0</td>
<td>18</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1/320</td>
<td>+ +</td>
<td>4200</td>
<td>1/40</td>
<td>+ +</td>
<td>0.0</td>
<td>22</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1/2</td>
<td>1/640</td>
<td>+ +</td>
<td>1/10</td>
<td>+ +</td>
<td>0.0</td>
<td>11</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1/10 240</td>
<td>+ +</td>
<td>1840</td>
<td>1/40</td>
<td>+ +</td>
<td>0.0</td>
<td>9</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1/1</td>
<td>1/20 480</td>
<td>+ +</td>
<td>1/640</td>
<td>+ +</td>
<td>6</td>
<td>40.5</td>
<td>64</td>
<td></td>
<td></td>
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</tbody>
</table>

+ + and + ++ = positive; - = negative

TABLE III T pallidum-specific IgG and IgA in the serum and CSF of patients with late syphilis with (Nos 1-6) and without (Nos 7-12) involvement of the central nervous system

<table>
<thead>
<tr>
<th>Patient No</th>
<th>IgG-FTA test Serum</th>
<th>IgG-FTA test CSF</th>
<th>IgA-SPHA test Serum</th>
<th>IgA-SPHA test CSF</th>
<th>IgA-FTA test Serum</th>
<th>IgA-FTA test CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+ +</td>
<td>+ +</td>
<td>1/16</td>
<td>1/2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>+ + +</td>
<td>+ +</td>
<td>1/8</td>
<td>1/2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>+ + +</td>
<td>+ +</td>
<td>1/4</td>
<td>1/2</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>4</td>
<td>+ + +</td>
<td>+ +</td>
<td>1/1</td>
<td>1/1</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>5</td>
<td>+ + +</td>
<td>+ +</td>
<td>1/1</td>
<td>1/1</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>6</td>
<td>+ + +</td>
<td>+ +</td>
<td>1/2</td>
<td>1/4</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>7</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
<td>+ +</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>+ +</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+ +</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>+ +</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>+ +</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

ND = not done; +, + +, + + + and + + + + = positive; - = negative

titre, 5-3) but in none of the patients without neurosyphilis (table III). IgA was consistently present in the CSF of the patients with neurosyphilis (mean titre, 2-0) but could not be detected in the CSF of those without neural involvement (table III).

Discussion

This study demonstrates differences in the distribution of CSF immunoglobulins in patients with neurosyphilis and in those without evidence of neurosyphilis. T pallidum-specific IgA in the CSF may indicate syphilitic involvement of the CNS.

The origin of CSF-IgG in patients with neurosyphilis has not yet been clarified. Since in this study IgA was detected in the CSF as well as in the serum at comparatively high titres, it may be transferred passively from the serum to the CSF or be produced in the CNS in close proximity to the CSF or both.

At first glance the presence of immunoglobulins in an infectious disease leads one to assume that
increased immune defence mechanisms are operative against the causative micro-organism. In this respect it is of interest that IgA has recently been shown to enhance the virulence of *Neisseria meningitidis* and *Candida albicans*, possibly by inhibiting IgG bactericidal activity. IgA seems to compete with IgG molecules at the Ig receptor sites on the target micro-organism. Since, however, IgA does not cause cytotoxicity by activating the classical complement pathway, the simultaneous presence of IgA and IgG, in fact, decreases the antibacterial effects of IgG.

Preliminary evidence thus indicates that the presence of *T pallidum*-specific IgA in the CSF of patients with neurosyphilis may be responsible for inhibiting the antitreponemal activity of CSF-IgG and thus play a role in the pathogenesis of neurosyphilis. Studies are in progress to investigate the role of IgA in the natural course of other stages of the disease.

References