**Comprehensive Viral Immunology of Multiple Sclerosis**

II. Analysis of Serum and CSF Antibodies by Standard Serologic Methods

Natalie E. Cremer, PhD; Kenneth P. Johnson, MD; George Fein, PhD; William H. Likosky, MD

- Sera and CSFs of 85 patients with multiple sclerosis (MS), 49 patients with probable MS, and 165 control patients with other neurologic diseases were assayed for antibodies to rubella, mumps, measles, parainfluenza 1 (strain 6/94), herpes simplex, cytomegalovirus, varicella-zoster, and vaccinia viruses. Methods included complement fixation (CF), hemagglutination inhibition (HI), and complement-dependent plaque reduction (CPR). Significant differences between the groups with MS and the control groups were higher serum antibody titers to measles virus in the groups with MS, higher proportion of patients with MS with CSF antibodies to measles, rubella, and vaccinia viruses, and greater percentage of patients with MS with more than one CSF viral antibody. Duration and severity of disease in the patients with MS were associated with presence of multiple CSF antibodies. Presence of CSF antibody was positively correlated with the height of the corresponding serum titer, yet a high serum titer did not ensure the presence of CSF antibody. Oligoclonal bands were present in the CSFs of equal proportions of patients with MS and without CSF viral antibody. Our data support the hypothesis of local antibody synthesis within the CNS. However, we favor the view that preprogrammed antibody-forming lymphocytes enter the CNS and then produce antibody either because of nonspecific polyclonal activation or because of failure of normal regulation.

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**SUBJECTS AND METHODS**

The criteria for selection of patients with MS and control patients, their ethnic background, age, and pertinent epidemiologic and clinical details have been presented in the first part of this series.

Serum specimens and CSF were drawn from groups of control patients and patients with MS at the same time and were received in the laboratory in sets of 30 to 40 specimens. Antibody assays were done on individual sets of control and MS specimens in the same run. All specimens were coded.

Antibodies were checked to measles, rubella, mumps, parainfluenza 1 (Sendai) (strain 6/94), cytomegalovirus, herpes simplex, and varicella-zoster viruses by standardized microcomplement fixation test (CF); to measles, rubella, mumps, and parainfluenza 1 (Sendai) viruses by standardized microhemagglutination inhibition (HI) test; to vaccinia virus by a complement-dependent plaque reduction test (CPR) modified from that of Takabayashi and McIntosh. Not all tests could be performed on all specimens because of anticomplementary or other nonspecific reactions with certain specimens. This fact will be reflected in the total number of specimens cited in various tables. Heparin manganous chloride, used for removal of nonspecific serum inhibitors to the rubella viral hemagglutinin, could not be used with CSF. Therefore, CSFs were untreated except for absorption with chicken erythrocytes of those specimens showing agglutination in control wells. All CSFs positive for rubella antibody by HI were also checked by the indirect fluorescent antibody test (IFA) using fluorescein-labeled antihuman IgG as described. Seventy-five percent also positive Immunoassays were determined by standard methods.

**Table 2**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Titer</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
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</tr>
</tbody>
</table>
five percent of CSFs positive by HI were also positive by IFI. Immunoglobulin class of viral antibodies was determined in 23 sera selected for study because of high measles HI titers (≥ 1:256). Twelve of the sera were from patients with MS, five from patients with probable MS, and six from control patients. The sera were centrifuged on a 10% to 40% linear sucrose gradient for 18 hours at 35,000 rpm. Fractions collected from the bottom of the gradients were checked by Ouchterlony test for immunoglobulin class using antisera specific for heavy chains of IgG, IgM, and IgA and by HI and CPR for viral antibodies known to be in the whole serum.

RESULTS

Serum Antibody Titers

Geometric mean serum titers (GMTs) of the four patient groups are given in Table 1 for all the standard serologic assays performed. In the computation of the GMTs, subjects who were negative for the specific virus at a dilution of 1:8 were assigned a titer of 1:4, the next lowest dilution. This may lead to overestimation of the GMT. For this reason, median titers for each group were also calculated. Differences between groups were tested using regression analysis with a dummy variable coding for group (for mean differences) and the Mann-Whitney U-test. The nonparametric analysis closely mirrored the differences between means. The group with definite MS as compared with the noninflammatory control group had a higher GMT for CF and HI antibodies to measles virus and a significantly lower GMT for CF antibodies to herpes simplex and cytomegalovirus. The group with probable MS as compared with the noninflammatory control group had a higher GMT for CF antibody to measles virus, but showed only a trend toward a higher GMT for HI antibody to measles virus (P < .05). There were no other significant differences that were consistent across the mean and median with the other serum assays between the noninflammatory control group and any of the other groups.

CSF Antibodies

Table 2 gives data on CSF antibody titers in the four patient groups. Cerebrospinal fluid antibody to rubella virus (HI assay) was present in approximately equal proportions of patients with MS and those with probable MS, and in a substantially lower proportion of noninflammatory control patients. Higher proportions of patients with MS and probable MS had CSF antibodies to measles virus (HI assay) and to vaccinia virus (CPR assay) than did the patients in the noninflammatory control group. The group with probable MS also had a higher proportion of patients with CSF CF antibody to measles virus as compared with the noninflammatory control patients. The higher incidence of CSF antibodies to these viruses resulted in higher proportions of patients with MS and probable MS who had antibodies to more than one virus in their CSF (Table 3).

The presence of CSF antibody to measles, rubella, or vaccinia virus was examined for association with the presence of CSF antibody to either of the other two viruses. As given in Table 4, there were no strong tendencies for these antibodies to appear together in patients with MS or probable MS.

<table>
<thead>
<tr>
<th>Table 1.- Geometric Mean Serum Titers*</th>
</tr>
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<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>HI</td>
</tr>
<tr>
<td>CF</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>HI</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>HI</td>
</tr>
</tbody>
</table>

*Expressed as reciprocal of dilution; SD as ± number of doubling dilutions from mean. Groups were compared using Mann-Whitney U-test.
1 CF indicates complement fixation; HI, hemagglutination inhibition; and CPR, complement-dependent plaque neutralization.
2 Higher than noninflammatory control group, P < .01.
3 Higher than noninflammatory control group, P < .001.
4 Lower than noninflammatory control group, P < .01.
5 Lower than noninflammatory control group, P < .001.
6 Lower than noninflammatory control group, P < .05.

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in the CSF, CSF IgG/albumin ratio, and serum antibody titers for the analogous assay. Table 5 gives medians for these measures. Comparisons between groups were computed using the Mann-Whitney U-test. For all assays, patients with positive CSF antibody assays had higher serum titers as compared with patients with negative CSF antibody assays. This was true across diagnostic groups. There was no relationship between presence of CSF antibody and presence of IgG oligoclonal bands in the CSF. However, patients with CSF antibody had higher IgG CSF levels than those without such antibody. This was true for all groups except the combined MS groups with CSF HI antibody to measles virus (trend only, \( P < .08 \)) and the combined control groups with antibody to vaccinia virus (no effect). Patients with positive CSF antibody assays in the control groups (but not in the groups with MS) had higher CSF albumin values as compared with patients with negative CSF assays for antibody to rubella, strain 6/94 and measles virus (\( P < .01 \)), and vaccinia virus (trend, \( P < .07 \)). Ratios of IgG:albumin followed from the IgG and albumin effects described, that is, highest CSF IgG:albumin ratios were seen in the group with MS with CSF viral antibodies.

**Serum-CSF Antibody Ratios**

The majority of serum-CSF ratios for all patients was less than or equal to 128, with the exception of ratios to measles virus HI antibody in the combined control groups and in the group with probable MS (Table 6). Analyses by the Mann-Whitney U-test on the three most prevalent CSF antibodies (measles, rubella, and vaccinia antibodies) in the groups with MS showed that only the geometric mean ratio for antibody to vaccinia virus of the groups with MS was significantly lower than that of the combined control groups (two-tailed \( P < .05 \), Table 7).

**Class of Serum Antibodies**

Antibody to measles virus was found only in the IgG fractions from sucrose gradients. Twenty-one of these sera also had antibody to rubella virus, 23 sera had antibody to vaccinia, and 20 sera had antibody to mumps virus. Antibodies to these viruses were also confined to the IgG fractions.

**COMMENT**

Preoccupation of MS research with analyses of serum and CSF antibodies to viruses stems from the observations of Adams and Imagawa\(^13\) on elevated serum and CSF antibody titers to measles virus in patients with MS as compared with titers in control patients. This finding has been observed in practically every study of patients with MS of this kind.\(^1,4,11\) In our study also, serum antibody titers to measles in the g with titeble 1). Th tant fserum an MS. Den antibody evidence that virus reported virus in t of some pence of re cause fell viral antil conside in their s infected c antibody. trol sera, antibody (\( \geq 1:256 \)), measles vi antibodies the IgG cli

Since th
to measles virus were slightly higher in the group with MS as compared with titers in the control groups (Table 1). This result was the only important finding relative to increased serum antibody titers in patients with MS. Demonstration of serum IgM antibody to a specific virus is taken as evidence for a current infection with that virus. Haire et al' and Pille et al reported IgM antibody to measles virus in the serum but not in the CSF of some patients with MS. The presence of rheumatoid factor in sera can cause false-positive IgM reactions for viral antibodies. However, Haire et al considered this problem eliminated in their studies by use of unfixed infected cells in IFA assays for IgM antibody. Our analysis of MS and control sera, selected because of high antibody titers to measles virus, showed that HI antibody to measles virus, as well as other viral HI antibodies present in the sera, were of the IgG class.

Since the original observations of Adams and Imagawa, other viral antibodies have been detected in the CSF. In our study, CSF antibodies to rubella, measles (HI antibody), and vaccinia viruses (CPR antibody) were more prevalent in groups with MS than in the noninflammatory control group (Table 2). These three viruses have the capacity of invading the CNS and precipitating disease, and, thus, the potential for involvement in MS pathogenesis.

Comparison of presence of CSF antibodies with clinical findings indicated there was no strong relationship between duration of symptoms and any of these antibodies, a finding also noted by Miyamoto et al who studied measles and vaccinia virus CSF antibodies. Severity of symptoms was positively related to CPR CSF antibody to vaccinia virus and to CF CSF antibody to measles virus, but not to HI CSF antibody to either measles or rubella viruses. Miyamoto et al reported CSF antibody to measles and vaccinia viruses most often in the chronic progressive form of MS as compared with the relapsing-remitting form of the disease. Similarly, Cendrowski et al found higher CSF antibody titers to measles virus in patients with a malignant course of the disease.

One reason for performing these serologic studies was that identification of antibody synthesis in the CNS might provide a clue to persistent virus(es) with pathogenetic importance in MS. Clarke et al suggested evaluation of serum/CSF antibody ratios for determination of local antibody synthesis. With an intact blood-brain barrier (BBB), ratios of 300 or greater are reported. Norby et al considered less than 100 to be subnormal. We have used a ratio of less than or equal to 128 as subnormal. By that criterion, the majority of patients with CSF antibody in both the MS and control groups had reduced ratios with all the viral antibodies tested. Exceptions were the ratios to measles virus of the group with probable MS and the combined control groups (Table 6). The geometric mean serum/CSF antibody ratio to vaccinia virus was the only ratio that was significantly lower in groups with MS than in control groups (Table 7) and was the only one that was reduced in close to 100% of the patients with MS and such antibody (Table 6). This is an unexpected finding. Both measles and rubella are prevalent, wild diseases in our society, whereas the main source of stimulation of antibody to vaccinia virus would be through vaccination, a practice in general use until recently. Others have also reported CSF antibody to vaccinia virus in patients with MS in the United States, but not from

Table 4.—Association of CSF Antibodies of Different Viral Specificities

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Negative</th>
<th>Positive</th>
<th>X²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI antibody to rubella virus</td>
<td>HI Antibody to Measles Virus</td>
<td>81</td>
<td>16</td>
<td>3.2</td>
</tr>
<tr>
<td>Positive</td>
<td>25</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HI antibody to vaccinia virus</td>
<td>Negative</td>
<td>84</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR Antibody to Vaccinia Virus</td>
<td>HI antibody to rubella virus</td>
<td>Negative</td>
<td>60</td>
<td>16</td>
</tr>
<tr>
<td>Positive</td>
<td>22</td>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HI indicates hemagglutination inhibition; CPR, complement-enhanced plaque reduction. This is for individual patients with multiple sclerosis (MS) and patients with probable MS.

Table 5.—Comparison of Medians of Various CSF Measures With Presence or Absence of CSF Antibody

<table>
<thead>
<tr>
<th>Assay</th>
<th>Presence of CSF Antibody, mg Protein/dL</th>
<th>Absence of CSF Antibody, mg Protein/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Positive Bands</td>
<td>IgG</td>
</tr>
<tr>
<td>Rubella, HI</td>
<td>37</td>
<td>74</td>
</tr>
<tr>
<td>Controls</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Parainfluenza (Sendai), HI</td>
<td>6/94, HI</td>
<td>17</td>
</tr>
<tr>
<td>Controls</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Measles, HI</td>
<td>28</td>
<td>91</td>
</tr>
<tr>
<td>Controls</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Vaccinia, CPR</td>
<td>28</td>
<td>93</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

*Antibody titers expressed as reciprocals of dilution.

**HI indicates hemagglutination inhibition; MS, multiple sclerosis; and CPR, complement-enhanced plaque reduction.

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generally practiced but where MS continued for the most part in the
a role in the pathogenesis of MS, a
uals beyond the age of
body titers in the top fifth of their
strain
number of patients with serum anti-
United States
investigators.16.21
observation has been made by other
body present in their CSF for each
virus. This was at least double the
assays), and for vaccinia virus (CPR
mirror high serum antibody titers but
of these patients had anti-
complement fixation.
Cytomegalovirus CF
Parainfluenza
Measles HI
Rubella, HI
HI 17/25 (68) 9/12 (75) 26/37 (70) 14/22 (64)
Vaccinia CPR 19/21 (90) 7/10 (70) 26/28 (93) 10/12 (83)
Measles HI 11/17 (65) 4/10 (40) 15/27 (56) 6/13 (46)
Paramyxovirus 1 (Sendai), HI 7/12 (58) 2/4 (50) 9/16 (56) 12/17 (71)
Cytomegalovirus CF ... (0) 0/1 (0) ... (0) 6/7 (86)

<table>
<thead>
<tr>
<th>Virus</th>
<th>Test†</th>
<th>Definite</th>
<th>Probable</th>
<th>Combined Groups</th>
<th>Combined Control Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella, HI</td>
<td>HI</td>
<td>17/25 (68)</td>
<td>9/12 (75)</td>
<td>26/37 (70)</td>
<td>14/22 (64)</td>
</tr>
<tr>
<td>Vaccinia CPR</td>
<td>CPR</td>
<td>19/21 (90)</td>
<td>7/10 (70)</td>
<td>26/28 (93)</td>
<td>10/12 (83)</td>
</tr>
<tr>
<td>Measles HI</td>
<td>HI</td>
<td>11/17 (65)</td>
<td>4/10 (40)</td>
<td>15/27 (56)</td>
<td>6/13 (46)</td>
</tr>
<tr>
<td>Paramyxovirus 1 (Sendai), HI</td>
<td>HI</td>
<td>7/12 (58)</td>
<td>2/4 (50)</td>
<td>9/16 (56)</td>
<td>12/17 (71)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>CF</td>
<td>... (0)</td>
<td>0/1 (0)</td>
<td>... (0)</td>
<td>6/7 (86)</td>
</tr>
</tbody>
</table>

Table 6.—Incidence of Reduced Serum/CSF Ratios

Multifocal sclerosis (MS) Combined Groups

<table>
<thead>
<tr>
<th>Virus</th>
<th>Test†</th>
<th>Definite</th>
<th>Probable</th>
<th>Combined Groups</th>
<th>Combined Control Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella, HI</td>
<td>HI</td>
<td>17/25 (68)</td>
<td>9/12 (75)</td>
<td>26/37 (70)</td>
<td>14/22 (64)</td>
</tr>
<tr>
<td>Vaccinia CPR</td>
<td>CPR</td>
<td>19/21 (90)</td>
<td>7/10 (70)</td>
<td>26/28 (93)</td>
<td>10/12 (83)</td>
</tr>
<tr>
<td>Measles HI</td>
<td>HI</td>
<td>11/17 (65)</td>
<td>4/10 (40)</td>
<td>15/27 (56)</td>
<td>6/13 (46)</td>
</tr>
<tr>
<td>Paramyxovirus 1 (Sendai), HI</td>
<td>HI</td>
<td>7/12 (58)</td>
<td>2/4 (50)</td>
<td>9/16 (56)</td>
<td>12/17 (71)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>CF</td>
<td>... (0)</td>
<td>0/1 (0)</td>
<td>... (0)</td>
<td>6/7 (86)</td>
</tr>
</tbody>
</table>

*Ratio of ≤ 128 considered to be a reduced ratio. With two exceptions, ratios for all other viral
antibodies in Table 2 were ≤ 128.
†HI indicates hemagglutination inhibition; CPR, complement-enhanced plaque reduction, and CF, complement fixation.
Number of patients with ratio ≤ 128/total number of patients with indicated CSF antibody percentage (% of ratios ≤ 128).

Table 7.—Serum/CSF Geometric Mean Ratios

<table>
<thead>
<tr>
<th>Virus</th>
<th>Test†</th>
<th>Definite</th>
<th>Probable</th>
<th>Inflammatory</th>
<th>Noninflammatory</th>
<th>Combined Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella, HI</td>
<td>HI</td>
<td>121 ± 1.44 (12)</td>
<td>181 ± 1.29 (4)</td>
<td>66 ± 0.39 (6)</td>
<td>136 ± 1.45 (11)</td>
<td>133 ± 1.39</td>
</tr>
<tr>
<td>Measles, HI</td>
<td>HI</td>
<td>118 ± 1.65 (17)</td>
<td>137 ± 1.60 (10)</td>
<td>64 ± 1.41 (2)</td>
<td>187 ± 1.21 (11)</td>
<td>125 ± 1.75</td>
</tr>
<tr>
<td>Vaccinia, CPR</td>
<td>CPR</td>
<td>43 ± 1.50 (21)</td>
<td>29 ± 1.35 (7)</td>
<td>91 ± 1.72 (2)</td>
<td>97 ± 1.84 (10)</td>
<td>39 ± 1.47</td>
</tr>
</tbody>
</table>

*Number of patients with CSF antibody. Geometric mean ratio ± SD (SD = ± indicated doubling dilutions from mean).
†HI indicates hemagglutination inhibition and CPR, complement-enhanced plaque reduction.
Numbers in parenthesis indicate number of patients.
§Multiple sclerosis < control, two-tailed Mann-Whitney U-test, P < .019.
et al." using imprint electroimmuno-
fixation showed that CSF viral anti-
bodies were in part oligoclonal. How-
ever, the oligoclonal bands demon-
strated by electrophoresis did not al-
tways coincide with the viral anti-
tibody oligoclonal bands identified by
imprint electroimmuno-fixation. Some
antibody bands occurred in positions
where no IgG bands were seen. The
conclusion was reached that the major
part of CSF IgG was not viral anti-
tibody of known specificity. Our results
are in agreement with this conclusion.
Oligoclonal bands were present in
about equal proportions of patients
with or without CSF-specific viral
antibody for which they were program-
med. Multiple sclerosis may involve a
basic defect in immunologic regula-
tion that allows continued or random
antibody production by B lymphocytes
nonspecifically attracted to the CNS.

(THIS IS PART 2 OF A THREE-PART STUDY.)

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