Interpretation of Cerebrospinal Fluid Protein Assays in Various Neurologic Diseases

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Albumin and immunoglobulin G (IgG) were determined in cerebrospinal fluid (CSF) and serum, and the CSF/serum albumin index (CSF × 10²/serum albumin concentration ratio) and IgG Index ([CSF/serum IgG]/[CSF/serum albumin]) were calculated. Data for these indices and oligoclonal banding are described in 23 cases of multiple sclerosis (MS), 19 of systemic lupus erythematosus (SLE), eight of sarcoidosis, 48 cases of miscellaneous disease, and 25 control patients with nonspecific complaints. Of the MS, SLE, and sarcoidosis patient groups, 8.5%, 26%, and 12.5% showed an abnormally high CSF/serum albumin index; 87%, 16%, and 0% an increased IgG index; and 87.5%, 42% and 0% showed positive oligoclonal banding. IgG Index and oligoclonal banding results for MS patients differed significantly from the sarcoidosis (p < .001) and SLE (p < .05) groups. When the CSF/serum albumin index is considered also, the control and sarcoidosis patient results differ significantly from the MS group (p < .001 and p < .01). A strong correlation between the IgG index and oligoclonal banding is implicated.

Additional Keyphrases: immunoglobulins, sarcoidosis, lupus erythematosus, multiple sclerosis, IgG index, CSF/serum albumin index, intrathecal IgG production

Particular challenges are presented in the laboratory-assisted evaluation of disorders and disease states involving the central nervous system (CNS).* Laboratory assays useful in this assessment include the IgG Index ([CSF/serum IgG] / [CSF/serum albumin]), the CSF/serum albumin Index (CSF × 10²/serum albumin concentration ratio) and electrophoresis for detection of possible oligoclonal banding (the presence in CSF of two or more bands of restricted electrophoretic mobility in the immunoglobulin region).

Interest in the IgG Index is based upon evidence that an increase of this ratio reflects intrathecal production of IgG (1, 2). Similarly, oligoclonal banding is considered evidence for abnormal immunoglobulin synthesis within the CNS (1–4). Most reports have documented an increased IgG Index or positive oligoclonal banding, or both, in multiple sclerosis (MS); however, these same reports indicate that similar patterns can also be found in 9 to 23% of patients with other neurologic conditions (1–6). The CSF/serum albumin Index is useful in assessing the integrity of the blood–CSF barrier (7). Diabetes mellitus, cervical spondylosis, inflammation of the spinal nerve roots, and decreased CSF flow are some clinical conditions under which this Index reportedly increases (7).

Our aim here was to describe the two indices and oligoclonal banding test patterns in well-defined cases of MS, systemic lupus erythematosus (SLE), and sarcoidosis. Such results for MS (1–6) and SLE (7) have been reported, but our analysis includes sarcoidosis patients in combination with these other groups, and further information is reported that can be used in the differential diagnosis of these maladies.

Materials and Methods

Patients. Twenty-five patients presenting with nonspecific complaints (e.g., tension headache, blurry vision, dizziness, etc.) served as controls. None had evident neurologic disorders as the basis for their symptoms. The study groups were: 23 patients having the clinical diagnosis of MS as determined by neurological evaluation; eight sarcoidosis patients with CNS involvement diagnosed by hilar lymphadenopathy, uveitis, erythema nodosum, and demographic features, with confirmatory biopsy of non-nervous system tissue in seven; and 19 SLE patients with CNS involvement classified by the preliminary criteria of the American Rheumatism Association (9). We also examined 48 patients with miscellaneous neurologic diseases. Diagnoses in this group included suspected MS, other demyelinating diseases, seizure disorders, viral encephalitis, organic encephalopathies of unknown etiology, Niemann–Pick disease, paraneoplastic cerebellar degeneration, polyneuropathy, Landry–Guillain–Barré syndrome, cervical spondylosis, meningeal carcinomatosis, myasthenia gravis, leukodystrophy, and CNS lymphoma.

Methods. Paired serum and CSF samples were collected within the same 24-h period and stored at −20 °C. Freeze/thaw cycles were avoided.

IgG and albumin in both CSF and serum were quantified by equilibrium (end-point) immunonephelometry, with an AutoAnalyzer II fluoronephelometer (Technicon Instruments Corp., Tarrytown, NY 10591). Antisera were purchased from Atlantic Antibodies, Scarborough, ME 04074, and diluted 25-fold with filtered isotonic saline. We calculated the IgG Index as follows:

\[ \text{IgG Index} = \frac{\text{CSF IgG/serum IgG}}{\text{CSF albumin/serum albumin}} \]

(Concentrations in mg/dL)

The normal reference interval used for the IgG Index was 0.34–0.66 (8). The CSF/serum albumin Index was calculated as follows:

\[ \text{CSF/serum albumin Index} = \frac{\text{CSF albumin/serum albumin}}{1000} \]

(Concentrations in mg/L)

Impairment of the blood–CSF barrier was estimated by using the magnitude of the CSF/serum albumin Index with the criteria of Schip and Felgenhauer (7): less than 9, no significant impairment; 9–14.3, slight impairment; 14.9–33.3, moderate impairment; 33.3–100, severe impairment; greater than 100, total breakdown.
We assessed oligoclonal banding by either isoelectric focusing electrophoresis on polyacrylamide, followed by immunofixation and peroxidase–antiperoxidase staining, or by agarose electrophoresis, staining with Naphthol Blue Black. Paired CSF and serum samples were run simultaneously to rule out banding due only to increased permeability of the blood–CSF barrier to immunoglobulin. We determined positive or negative oligoclonal banding by visual inspection of the stained gels. All probabilities were determined by use of Chi-square analysis.

![Image 1](chart1.png)  
**Fig. 1.** Data on multiple sclerosis patients  
@, oligoclonal banding positive; O, oligoclonal banding negative; A, oligoclonal banding not done. In all Figures, the lines indicate normal reference intervals

Of the 23 MS patients (Figure 1), data for 18 fell within the region consistent with an interpretation of local CNS synthesis of IgG. None of the MS patients showed only an increase in blood–CSF barrier permeability, but two of them show evidence of combined permeability and intrathecal IgG synthesis. Oligoclonal banding was positive in 14, negative in two, and not performed (insufficient sample) in seven members of this group.

Data for the SLE patients are plotted in Figure 2. Evidence of intrathecal IgG synthesis is seen in three patients; four show slight to moderate increases in blood–CSF barrier permeability. Two members of the SLE group show increases in both blood–CSF permeability and IgG synthesis in the CNS. Oligoclonal bands were detected in eight of the 19 patients in the SLE group.

Figure 3 shows our results for the eight cases of sarcoidosis. One showed evidence of increased IgG synthesis in the CNS; two showed slight increases in blood–CSF barrier permeability. None of these cases evidenced oligoclonal bands in their CSF.

![Image 2](chart2.png)  
**Fig. 2.** Data on systemic lupus erythematosus patients  
@, oligoclonal banding positive; O, oligoclonal banding negative

**Results**

Figures 1, 2, and 3 show the IgG Index vs the CSF/serum albumin Index for the MS, SLE, and sarcoid-disease patients, respectively. The normal reference intervals are indicated.

![Image 3](chart3.png)  
**Fig. 3.** Data on sarcoid-disease patients  
@, oligoclonal banding negative (all patients)

Table 1 gives the test-pattern relationship of the CSF/serum albumin Index, oligoclonal banding, and IgG Index for individual patients in the groups with defined MS, sarcoidosis, and SLE. Consideration of group B (positive oligoclonal banding; increased IgG Index; CSF/serum albumin Index within reference interval) shows MS patients to be significantly more likely to controls (p < .001) or sarcoid patients (p < .01) to have this test-pattern result. We saw no significant difference between the MS and SLE patients regarding group B. The other three test-group comparisons fail to significantly discriminate sarcoidosis or SLE from controls or each other.

If the CSF/serum albumin Index is eliminated from the
Table 1. Accumulated Patient and Test Data

<table>
<thead>
<tr>
<th>Test result</th>
<th>No. cases</th>
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<tbody>
<tr>
<td>Group</td>
<td>Oligo+a</td>
</tr>
<tr>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
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<td>C</td>
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above consideration, groups A and B, C and D, E and G, and F and H of Table 1 are respectively combined. Positive oligoclonal banding and an increased IgG Index significantly distinguishes the MS and SLE patient groups (p < .05), and MS and sarcoidosis are better resolved (p increases from <.01 to <.001 by this analysis). Sarcoïd and SLE patients did not differ significantly in any two test comparisons.

Discussion

Our data provide further evidence of intrathecal IgG production in MS patients: 87% of this group shows an increased IgG Index (20 to 23) and positive oligoclonal banding (14 of 16). In addition, a significant difference between the control and MS groups is seen when the CSF/serum albumin Index, IgG Index, and oligoclonal banding are considered (p < .001). Nine percent of MS patients (two of 23) show a slight increase in blood–CSF barrier permeability, but only in association with increased IgG synthesis in the CNS. Immunoglobulin production in the CNS is well described in MS (2, 3, 5), and our study provides additional support for proposed etiologies involving IgG production in the CNS.

The sarcoidosis patients showed only a slight increase in the CSF/serum albumin Index (two of eight) and slight increase in the IgG Index (one of eight). Evidently neither blood–CSF barrier permeability or CNS IgG synthesis is an important feature of this disorder. Three of our SLE patients show evidence only of IgG synthesis within the CNS, four showed increased blood–CSF barrier permeability, and two showed both. Intrathecal IgG synthesis was unrelated to either the nature (focal vs diffuse) or severity of CNS manifestation in SLE. Detailed clinical correlations, reported separately, suggest that increases in blood–CSF barrier permeability are associated with diffuse, major CNS injury, such as encephalopathy with coma, transverse myelopathy, or paraparesis (10).

Our data emphasize the various CSF protein patterns that are seen in selected neurologic disorders. Overall, there is a strong correlation between positive oligoclonal banding and an increased IgG Index, suggesting that there is an ongoing humoral immune response—particularly in MS and SLE, but also in certain patients with CNS infections or paraneoplastic CNS disease. Patients with sarcoidosis showed little evidence of such an ongoing immune process.

References