Measurement of IgG and Albumin Content of Cerebrospinal Fluid, and Its Interpretation

Karin Ganrot and Carl-Bertil Laurell

A high correlation \( (r = 0.85) \) normally exists between the concentration of albumin and of IgG in cerebrospinal fluid (CSF). The correlation is still better \( (r = 0.96) \) if the concentrations of the two proteins are also measured in plasma and the CSF/plasma ratios compared for albumin and IgG. The scatter diagram for these ratios in persons without disease of the nervous system is most useful as a reference when differentiating between local IgG production in the subarachnoid space and an increase in CSF protein for other reasons. The analysis can be performed on less than 0.1 ml of CSF, in contrast to agarose-gel electrophoresis, for which 5–10 ml is necessary.

Additional Keyphrases: blood–brain barrier • disease of the nervous system • diagnostic aid • multiple sclerosis • electrophonnoassay • subarachnoid IgG production • normal values

Quantitative measurement of IgG in cerebrospinal fluid (CSF) was originally introduced by Kabat et al. (1) to reveal immunoglobulin production in the subarachnoid space and the brain. A normal IgG concentration in CSF does not exclude an abnormal local subarachnoid IgG production, because an oligoclonal or monoclonal electrophoretic IgG pattern may sometimes be found in CSF together with an IgG concentration that still is within the relatively wide "normal range." This range gets more narrow when the ratio IgG/total protein (2) or, still better, IgG/albumin (3) in the CSF of normal individuals is used as a reference to discriminate for local IgG synthesis. Local, abnormal immunoglobulin production in or near the subarachnoid space is reported to be best detected by comparing the electrophoretic Ig pattern in CSF and in plasma. This is preferably done by electrophoresis on agar gel (4, 5) or agarose gel (6). The local IgG production may be oligo- to polyclonal, which makes it difficult to recognize the local response, especially when the blood–CSF barrier is impaired and such impairment is accompanied by a local immunocyte reaction.

The occurrence of local immunoglobulin production is of considerable diagnostic significance, and so more quantitative methods requiring less CSF than for electrophoretic analysis are needed to differentiate between IgG increase secondary to increased permeability and (or) local production.

The ratio between the concentrations of specific proteins in CSF and serum is highly correlated with total CSF proteins, both normally and when there is only a slight increase in the total proteins (7). The ratio between the concentrations of IgG and albumin in CSF and in plasma has been proposed by Delpuch and Lichtblau (8) as a reference index to discriminate between local IgG production and IgG increase of other origin. Their index includes a correction for variations of IgG and albumin in plasma and should therefore give higher discrimination than earlier indexes. This approach seemed logical to us, and we tested the information obtainable from a fast, immunochemical analysis of the relative concentrations of these proteins in CSF and plasma and compared it with results of electrophoretic analysis.

Materials and Methods

Clinical Material

The control material consisted of 54 men and women between 19 and 76 years of age (mean, 55), without symptoms or signs of neurological disease. Samples of CSF were obtained in connection with induction of spinal anesthesia for inguinal herniorrhaphy, prostatectomy, or operation of varicose veins of the legs.

The group of patients with multiple sclerosis consisted of 12 women and eight men, 17 to 62 years old (mean, 40). The diagnosis had been made on the basis of neurological symptoms indicating multiple lesions of the central nervous system. Paresis, tactile disturbances, and ataxia generally occurred sometime during the frequently remittent course of the disease. Single or recurrent attacks of optic neuritis were common. The patients had had the disease for six months to 20 years. The CSF was sent to our laboratory for examination of the electrophoretic pattern.
Methods

Total protein was determined according to Lowry et al. (9), with tyrosine as the standard (0.52 mg of tyrosine per liter, corresponding to 2.00 g of protein per liter). Albumin was analyzed by electroimmunoassay (10) and IgG with a modified assay (11). The analytical errors were 3 and 5%, respectively. Total protein was measured first, and the value obtained served as a guide to dilution of the samples in the electroimmunoassay so as to obtain similar heights of the rockets for plasma and CSF, which were run side by side to diminish analytical error.

Results

Table 1 shows results of analysis of albumin and IgG in the plasma and CSF of the 54 control subjects and in the 20 subjects with multiple sclerosis. The distribution of albumin and IgG in CSF was positively skewed in the control group, and so the log mean has also been calculated. Figure 1 shows how ratios between albumin in CSF and in plasma are distributed in relation to age. The 14 controls in the age interval 19–45 years had a mean ratio of 0.00563 as compared with 0.00842 for the controls between 50 and 85 years. The limited material with its wide range of variation gave a low correlation (r = 0.41 and P < 0.01) between age and the albumin ratio.

Figure 2 gives the relation between IgG and albumin in CSF. For the controls, r = 0.85.

Figure 3 gives the relation between the CSF/plasma ratios for IgG and albumin. This correlation is closer (r = 0.96) and significantly different (P < 0.001) from the correlation between albumin and IgG in CSF. The close correlation in the control group contrasts with the low corresponding correlation (r = 0.51) in the group of subjects with multiple sclerosis. Electrophoretic agarose gel analysis of CSF showed one or more abnormal tiny bands in the Ig zone of these patients, but not in the controls.

### Table 1. Albumin and IgG Concentrations in Cerebrospinal Fluid and in Plasma of 20 Subjects with Multiple Sclerosis, Compared with 54 Controls

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Control group</th>
<th>Multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF, mg/liter</td>
<td>mean ± SD</td>
<td>304 ± 126</td>
</tr>
<tr>
<td>(log mean)</td>
<td>(280)</td>
<td>(169)</td>
</tr>
<tr>
<td>range</td>
<td>100–600</td>
<td>100–400</td>
</tr>
<tr>
<td>plasma, g/liter</td>
<td>mean ± SD</td>
<td>40.8 ± 6.0</td>
</tr>
<tr>
<td>range</td>
<td>30–50</td>
<td>33–51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IgG</th>
<th>Control group</th>
<th>Multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF, mg/liter</td>
<td>mean ± SD</td>
<td>20.6 ± 14.0</td>
</tr>
<tr>
<td>(log mean)</td>
<td>(23.3)</td>
<td>(63.2)</td>
</tr>
<tr>
<td>range</td>
<td>8–64</td>
<td>28–144</td>
</tr>
<tr>
<td>plasma, g/liter</td>
<td>mean, SD</td>
<td>9.3 ± 1.8</td>
</tr>
<tr>
<td>range</td>
<td>6–13.2</td>
<td>6–13.2</td>
</tr>
</tbody>
</table>

Discussion

Values for CSF albumin concentration vary less between laboratories than values for total proteins, because methods and standards for calibration differ less from one laboratory to another. Albumin is principally produced by the liver and its subarachnoid synthesis is generally considered negligible. CSF albumin was therefore chosen here as a reference protein. The CSF albumin concentration is assumed to give some integrated information about changes in the permeability of the blood–CSF barrier and cerebrospinal fluid turnover. This implies, for instance, that the albumin concentration of plasma will influence the albumin concentration of CSF. The same holds true for IgG. Albumin normally has an equilibration time of about five days between plasma and CSF (12), and so changes in its concentration in plasma will be reflected in the CSF albumin only after some delay. The ratio of CSF albumin to plasma albumin will therefore reflect the permeability and CSF formation slightly better than CSF albumin itself in nonacute changes of the plasma albumin. This is still more important in disorders accompanied by a wider range of albumin variation than was the case for our patient material.
The ratio between albumin in CSF and albumin in plasma has been tested as a reference, in an attempt to differentiate between local IgG production in or near the subarachnoid space and increased passage of IgG from blood and (or) water loss of CSF as causes of increased protein concentration of CSF. In our control group a higher correlation was found between CSF/plasma ratios for albumin and IgG \((r = 0.96 \text{ vs. } 0.85)\) than on direct comparison of their concentration. This high co-variation is of physiological interest in view of the wide spread in values for IgG and albumin, respectively, in CSF (Table 1).

The high correlation between the albumin and IgG ratios may suggest that changes in the absolute concentration of the two proteins in CSF usually depend more on the relative turnover of water and of proteins than on differences in permeability for proteins that are in the size range of albumin and IgG. The grouping of the results according to the subject’s age (Figure 1) suggests an age dependence of the ratios between albumin and IgG, but a larger clinical material is desirable before the age dependence of the protein concentration in CSF can be confidently assessed.

Six of the 20 patients showed normal IgG values for their CSF if we ignore the relation between IgG and albumin as an expression of normal variation in permeability and production rate of CSF. However, by the plotting system used, control values and values for persons with multiple sclerosis were discrete (Figure 3). As judged from the albumin values, permeability and fluid exchange was normal in the cases of multiple sclerosis. The electrophoretic results of CSF analyses compared with those of plasma gave the expected support for the diagnosis of subarachnoid space IgG production in all the patients. Electrophoretic analysis is claimed to be the method of choice when multiple sclerosis is suspected (13), but the quantitative immunologic analysis can be run on about .01 the amount of CSF necessary for electrophoretic analysis. In meningitis and encephalitis, increased permeability and local Ig response are often combined. The plotting system shown here (Figure 3) facilitates recognition of local Ig response and increased protein leakage secondary to (e.g.) inflammatory reaction, as will be corroborated in a forthcoming paper.

This investigation was supported by a grant from the Swedish Medical Research Council (Project No. B74-13X-581-10C).

References