Immunoglobulins in Cerebrospinal Fluid in Various Neurologic Disorders
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We determined the concentrations of immunoglobulins A, G, and M in cerebrospinal fluid of 16 patients suffering from multiple sclerosis, 13 with non-bacterial meningitis, 10 with stroke syndrome, and 13 with epilepsy. The differences in concentrations of immunoglobulins in these groups were remarkable in the patients with multiple sclerosis, meningitis, or stroke syndrome. We propose that the determination of the absolute immunoglobulin content in cerebrospinal fluid is of greater significance than the relative immunoglobulin concentration.

Additional Keyphrases: multiple sclerosis • nonbacterial meningitis • stroke syndrome • epilepsy

More than 35 years have passed since Kabat et al. (1), using the Tiselius electrophoresis method, first noted that the γ-globulin content of cerebrospinal fluid (CSF) was increased in patients with multiple sclerosis and neurosyphilis. Since then, considerable research has been directed towards finding abnormalities of the CSF immunoglobulins G, A, and M (IgG, IgA, and IgM), which are characteristic of various neurologic disorders, especially multiple sclerosis, and infective diseases of the central nervous system. Early in these studies Schneck and Glaman proposed (2) that the determination of the relative concentration of immunoglobulins in CSF (i.e., expressed in percent of total CSF protein concentration) is of greater significance than the absolute immunoglobulin content (mg/L).

The purpose of this paper is to determine the concentration of IgG, IgA, and IgM in CSF in various established neurologic diseases and to discuss their possible role in the pathogenesis of these disorders.

Materials and Methods
Cerebrospinal fluid was sampled by lumbar puncture of 52 patients who were divided into four groups.

Group 1 was 16 patients, 21 to 58 years old (mean, 33), suffering from multiple sclerosis diagnosed according to the following criteria: (a) age of onset between 15 and 45 years of age, (b) signs indicative of damage to at least two different parts of the central nervous system, and (c) a course of disease with at least two exacerbations and one remission.

Group 2 was 13 patients, 6 to 42 years old (mean, 27), suffering from non-bacterial meningitis.

Group 3 was 10 patients, 35 to 77 years old (mean, 48), with stroke syndrome.

Group 4 was 13 patients, 22 to 53 years old (mean, 33), with idiopathic epilepsy (grand mal).

The control group consisted of 21 persons, 13 to 77 years old (mean, 34), suffering from minor psychoneurotic disorders, whose CSF leukocytes were less than 5/μL and whose total CSF protein concentration was less than 450 mg/L.

Cell count was routinely performed and the cells were separated by a gentle centrifugation; after the total protein was measured, specimens were stored at -20 °C. We estimated CSF immunoglobulins by the single radial immuno-diffusion method of Mancini et al. (3), using Behringwerke AG-Marburg/Lahn, 67019 Scopitto (l'Aquila) standard sera with plates covering the higher ranges.

Statistical analysis was by Student's t-test.

Results
The results of this study, given in Table 1, are summarized as follows:

1. Total CSF protein in the control group was 223 ± 89 (SD) mg/L; in multiple sclerosis, it was 388 ± 179 mg/L, which is statistically significant. Also statistically significant was the increase in total CSF protein in non-bacterial meningitis. In stroke syndrome and epilepsy, however, the difference was not significant.

2. Absolute concentration of IgG in CSF of controls was 42 ± 21 mg/L, which differed significantly (p < 0.025) from that obtained from multiple sclerosis patients. The increase in CSF IgG was also statistically significant in non-bacterial meningitis and in stroke syndrome, but not in epilepsy (60.6 ± 35 mg/L).

3. The relative concentration of IgG in CSF of healthy individuals was not significantly different (p > 0.1) from that in patients with multiple sclerosis, non-bacterial meningitis, stroke syndrome, or epilepsy.

4. We detected IgA in only four of 21 cases in the control group (19%), but more often in the patient groups (present in 31 to 54% of the subjects; see Table 1). We could not detect IgM in the controls or in the multiple sclerosis, stroke syndrome, and epilepsy groups, and in only one case of non-bacterial meningitis.

Discussion
Previous reports dealing with CSF immunoglobulins in various neurologic diseases have focused attention on the concentration of CSF-IgG in demyelinating and infective diseases of the central nervous system (1, 2, 4–7). Some investigators suggest that the relative CSF-IgG concentration is of greater importance than the absolute CSF-IgG content (2). Our study does not support this suggestion: we did not find any differences in the relative CSF-IgG concentration, even in cases where the absolute CSF-IgG concentration was significantly increased.

We were able to confirm previous observations of increased CSF-IgG in patients with multiple sclerosis (2,6–8), but we dispute the finding that the relative concentration of CSF-IgG is significantly increased in these patients.

We believe that the increase in concentration of CSF-IgG is connected with the increase in total CSF protein; consequently, the ratio of IgG to total protein does not change significantly. This increase could be attributed to a migration of protein from serum to CSF because of damage to the blood–CSF barrier.

The increased frequency of detection of CSF-IgA in multiple sclerosis (seven of 16 cases, or 44%) is interesting and agrees with previous observations (2, 7, 9). This increase may be expected to occur in cases with damage to the blood–CSF barrier and increased total concentration of protein in CSF, CSF-IgA concentration increasing proportionally with the increase of total concentration of CSF protein (10). Further-

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more, an increased rate of synthesis cannot be excluded, because in vitro synthesis of IgA has previously been demonstrated with lymphocytes from the CSF of one patient with multiple sclerosis (11).

That CSF-IgM concentration was less than 2.5 mg/L (undetectable) is in agreement with previous observations of Link and Müller (7), who used radial immunodiffusion, and Schneck and Glaman (2), who used electroimmunodiffusion; they report that increased absolute CSF-IgM concentration rarely occurs in this disorder.

The finding of the increased concentration of IgG in CSF in non-bacterial meningitis is in agreement with the observations of Link and Müller (7). Also in this case we found no changes in the relative concentration of CSF-IgG. The detection of IgA in seven of 13 cases and IgM in one of the cases is of special interest. Further investigation is required before conclusions can be drawn about the pattern of alterations in immunoglobulin concentrations in CSF during the course of this infection.

The observation of increased IgA and IgG in CSF in stroke syndrome is in agreement with previous finding of Schneck and Glaman (2), who found increased IgA and IgG of 72% and 61%, respectively, in the CSF of these patients. There is at present no explanation for this increase.

In epilepsy we did not observe any disturbances in total protein, IgG, or IgM in CSF. On the other hand, only four of 13 patients displayed IgA.

In conclusion, we state that alterations in immunoglobulins in CSF are common in neurologic disorders, especially multiple sclerosis and infections of the central nervous system, although the exact pattern of these differences, as well as their cause, significance, and diagnostic value, presents questions without answers at this time. Further investigation to clarify these changes could contribute to a better diagnosis and possibly better treatment of various neurologic diseases.

References