Cerebrospinal fluid immunoglobulin quotients, kappa/lambda ratios, and viral antibody titres in neurological disease

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SYNOPSIS A description has been given of cerebrospinal fluid (CSF) immunoglobulins in 355 patients with demyelinating, infectious, neuropathic, and other neurological disorders. An increase in the CSF IgG/albumin quotient was observed in 19/36 (53%) cases of definite multiple sclerosis (MS), in 13/47 (28%) cases of probable or possible MS, in 6/9 (67%) cases of proven herpes simplex viral encephalitis (HSVE), in 3/4 (75%) cases of neurosyphilis, in 1/1 case of subacute sclerosing panencephalitis (SSPE), in 2/9 (22%) cases of other central nervous system infections, and in 2/12 (17%) cases of polyneuritis when compared with a group of 236 patients having other neurological disorders. In contrast, a relative increase in the CSF IgA or IgM was seen only in some of the patients with central nervous system infections.

It was also found that the quotient CSF/serum IgG, expressed as a percentage of the CSF/serum albumin, was better in distinguishing patients with definite or suspected MS from those with other neurological disorders than the quotients IgG/albumin or IgG/total protein.

The CSF κ/λ ratio and the CSF and serum complement-fixing antibody titre to measles and herpes simplex virus were measured in many of the patients. In general, abnormalities of these measurements were associated with raised IgG/albumin quotients. However, in eight patients with definite or suspected MS, a normal IgG/albumin quotient was found with abnormal CSF κ/λ ratios (6 cases) or abnormal CSF titres of measles antibody (7 cases). In addition, two patients with HSVE had normal IgG/albumin ratios but detectable herpes antibody in the CSF.

These findings suggest that the measurement of the relative concentration of CSF immunoglobulin in combination with the κ/λ ratio and antibody titre to various viruses may supplement each other in the endeavour to detect central nervous system immunoglobulin synthesis in neurological diseases.

In normal individuals, immunoglobulin in the CSF is derived from the plasma by diffusion across the blood/CSF barrier (see Schultze and Heremans (1966) Chapter 3 for review). Rosenthal and Soothill (1962) have shown that the quantity of this CSF immunoglobulin is dependent on the serum immunoglobulin concentration, the molecular size of the immunoglobulin, and the permeability of the blood/CSF barrier. Thus for healthy individuals IgM is totally excluded from the CSF owing to its large size and low plasma concentration but may be present in conditions in which a gross defect in the

blood/CSF barrier has occurred or where a high serum level exists.

However, in the last two decades a considerable amount of clinical and experimental evidence has accumulated which strongly suggests that immunoglobulin may be additionally synthesized in the central nervous system (CNS) in certain demyelinating and infectious neurological diseases (reviewed by Tourtellotte (1970)).

The CNS-produced immunoglobulin may be indirectly assessed by measuring the CSF immunoglobulin. However, in doing this it is necessary to correct for the permeability of the blood/CSF barrier in order to account for the immunoglobulin derived

from the plasma. Tourtellotte (1970) and others have shown that the permeability of the blood/CSF barrier is accurately reflected by the CSF total protein or albumin level, and thus most investigators have related the absolute CSF immunoglobulin level to the CSF total protein or albumin level in order to derive a relative immunoglobulin concentration. If this relative concentration (or immunoglobulin quotient) is raised, this has been taken to indicate the local synthesis of immunoglobulin within the CNS.

The aim of the present study has been to measure the CSF immunoglobulin/albumin quotient in patients suffering from a variety of neurological disorders and to compare groups of patients with demyelinating, infectious, and polyneuritic diseases with the remaining patients. An endeavour has also been made to find which CSF quotient, out of several which have been described, is best at distinguishing the different groups. In addition, in certain patients the IgG/albumin quotient has been compared with the CSF kappa/lambda ratio and the CSF measles, mumps, and herpes simplex antibody titres to see the relationship between these measurements and to determine whether a further refinement in the separation between these diagnostic groups can be obtained.

Patients

The CSF was obtained from 355 patients suffering from a variety of neurological disorders. At the end of the period of study the clinical and laboratory details were reviewed from the case notes and a comparison was made with the CSF findings.

There were 236 patients who formed the neurological control group. They consisted of 92 females and 141 males (3 were unknown) and had an average age of 46.4 years. Thirty-eight of these patients had cerebrovascular disease, 14 degenerative disease, 17 epileptic disorders, 17 senile dementias, 41 cervical and lumbar osteopathies, 18 CNS tumours, 26 neuroses or different forms of headache, 53 had other disorders, and 12 were undiagnosed.

There were 83 patients who had or were suspected of having MS. These patients were subdivided into two groups—the first consisting of patients with definite MS and the second of patients with probable or possible MS. This subdivision was, in general, based on the diagnostic criteria of McAlpine *et al* (1972). Thus patients with definite MS had evidence of multiple sites of CNS involvement associated with a history of a previous acute neurological episode followed by improvement and then one or more relapses. There were 23 females and 13 males in this subdivision; their mean age was 36.7

(range 17–60) years, the mean duration of the disease was 5.8 years (range 1 week–28 years), and the mean number of neurological episodes was 3.1 (range 2–6). There were 25 females and 22 males with probable or possible MS. The mean age was 40.7 (12–64 years), the mean duration 3.7 years (1 week–22 years), and the mean number of attacks 1.8 (1–8). For both MS groups over 80% of the patients were studied during an active phase of the disease. The remaining patients were either in clinical remission or had the chronic progressive form of the disease.

Twenty-four patients suffered from a CNS infection. Patients were not included in this category unless an infectious agent was positively identified or strongly implicated. Nine patients had HSVE, the diagnosis being proven by viral isolation from brain biopsy or CSF, positive immunofluorescence, or a rising titre to herpes simplex virus (HSV) in both the serum and CSF. Five patients had bacterial meningitis, four patients had neurosyphilis, two patients had tuberculous meningitis, two patients had herpes zoster meningoencephalitis, and one patient each had SSPE and a cerebral abscess.

The remaining 12 patients had a polyneuropathy including four with characteristic features of the Guillain-Barré syndrome.

Methods

CEREBROSPINAL FLUID

CSF was obtained by the lumbar route in all patients. These specimens consisted of the majority received by the laboratory over a one-year period. However, seven specimens from patients with HSVE had been collected and stored at -20°C over an eight-year period. Specimens of CSF were eliminated if heavily bloodstained (> 2000 red blood cells/ mm^3). The CSF cell count was routinely performed and the cells were separated by gentle centrifugation. The total protein was then measured and the specimens were stored at -20°C for future protein estimation. This was performed in large batches within six months of storage.

Serum was available for study from 62 of the patients. It was collected at the time of the lumbar puncture and studied simultaneously with its corresponding CSF.

CSF TOTAL PROTEIN

The CSF total protein was measured using a modification of the U-V spectrophotometric method of Waddell (1956). The CSF extinction at 215 and 225 μm was measured and compared with a standard protein preparation and the mean of the two readings was calculated.

PROTEIN MEASUREMENTS

CSF and serum albumin, IgG, IgA, IgM, and CSF κ/λ ratio were measured using the single radial immunodiffusion method of Mancini *et al* (1965). Plates were prepared using Wellcome antihuman IgG, IgA, and IgM, Behringwerke antihuman albumin, and Dakapatts antihuman κ and λ . The World Health Organisation reference serum 66/97 was used as a standard for the immunoglobulin levels (and converted to mg% using the formulae of Humphrey and Batty (1974) and for the κ/λ ratio (where it was arbitrarily assigned a ratio of 1.35). Behringwerke standard serum no. 1730 was used as a standard for albumin.

The lowest limit at which immunoglobulin could be accurately measured using this method was 0.05 iu/ml for IgG and IgA and 0.1 iu/ml for IgM. The coefficient of variation for the measurement of albumin and IgG was less than 10%. Each value for albumin and IgG was the mean of duplicate measurements while only single estimations were performed for the other proteins.

VIRAL ANTIBODIES

Complement fixing antibodies against measles, mumps, and HSV were measured in serum and CSF using the method of Smith *et al* (1967). If possible the CSF/serum antibody titre ratio was used in the assessment of antibody in the CSF. In CSF associated with an intact blood/CSF barrier no antibodies against these viruses are normally detected by this method.

ANALYSIS OF RESULTS

Protein concentrations in the healthy population approximate to a normal distribution when plotted on a logarithmic scale (Weeke and Krasilnikoff, 1970). In addition, a close approximation to a normal distribution was obtained for the IgG/albumin quotient and kappa/lambda ratio of the neurological control group when plotted on a log scale. Accordingly, all quotients have been plotted using this scale and the means and standard deviations calculated from the log of the quotients. Correlation coefficients between two variables have been calculated on the log measurements using the method of least squares.

Results

IgG/ALBUMIN QUOTIENT (see fig 1)

Neurological control group

The mean + 2 standard deviations (M + 2SD) of the CSF IgG/albumin quotients obtained for 236 patients in this group was 13.9 + 14% (fig 1).

Six patients had a quotient greater than the M + 2SD. Two of these had long-standing dementia, and in one an elevated κ/λ ratio (*vide infra*) and a mild CSF pleocytosis (6 lymphocytes/mm³) were also found. A third patient had a low CSF albumin but a normal CSF IgG concentration.

Of the 10 patients with quotients less than the M - 2SD (6.9%, fig 1), two were children with hydrocephalus. A third infant of 2 months of age was also noted with a low quotient and predictably had low levels of serum and CSF IgG. The remaining seven patients had a variety of unrelated diseases.

The M + 2SD of the IgG/albumin quotients of a group of 36 patients suffering from myelographically defined cervical spondylosis with myelopathy or lumbar disc herniation was 14.5 + 10.2%. If 24.7% is taken as an upper limit for this latter group, this is similar to the value (27.9%) obtained for all the neurological control patients combined.

Patients with multiple sclerosis

The IgG/albumin quotient was elevated in 19/36 (53%) of definite and 13/47 (28%) of probable or possible cases of MS when compared with the M + 2SD of the neurological control group (fig 1).

The M + SD for the mononuclear leucocyte cell counts in the CSF for patients with definite MS was 12.5 (range 0.81/mm³) and for patients with suspected MS, 4.6 (0.21/mm³). Twenty-one out of 34 (62%) of the definite MS patients and 15/39 (39%) of the suspected MS patients had CSF mononuclear leucocyte counts in excess of 5 cells/mm³. A significant correlation was seen between this cell count and the IgG/albumin quotient when both MS groups were combined ($r = 0.38$, $p = 0.01$) but not for the definite MS group taken alone. Significant correlations were also seen for both groups combined between the IgG/albumin quotient and the duration of the disease ($r = 0.22$, $p = 0.05$), and the reciprocal of the albumin level ($r = 0.24$, $p = 0.04$). These correlations were not significant, however, in the definite MS group alone. No correlation was observed with the age of the patients in either group or in both groups combined.

Patients with CNS infection

Several CSF specimens from patients comprising the CNS infection group had elevated IgG/albumin quotients (fig 1). Of interest was the finding that 6/9 patients with proven HSVE had elevated quotients. Of the three CSF specimens with normal quotients, one was from a patient who had survived the encephalitic episode for over a year while another was from a patient whose encephalitis had been present for only two days. The clinical details of the third patient were unobtainable. The CSF of the remain-

Fig 1 IgG/albumin quotient (expressed as a percentage) obtained for 355 patients with various neurological diseases. The vertical line represents the mean $\pm$ 2 standard deviations ($M \pm 2SD$) of the quotient for the neurological control group. The $M + 2SD$ has been taken as the upper limit in the comparison of the various groups. The proportion of patients with elevated quotients has been indicated for each diagnostic group.

ing six patients were all obtained between the 12th and the 200th day of the illness.

Three out of four patients with neurosyphilis had elevated quotients. The single patient with a normal quotient had been twice treated for tabes dorsalis over a 20-year period. Two other patients were untreated while the remaining patient had been diagnosed and treated seven years previously.

Three other patients, one with a cerebral abscess, one with SSPE, and one with bacterial meningitis, had elevated quotients.

Patients with polyneuropathies

Two patients out of 12 in this group showed an elevated IgG/albumin quotient (fig 1). In one of these a small monoclonal IgG band was noted in the corresponding serum.

QUOTIENT USED TO ADJUST FOR VARIATIONS IN BLOOD/CSF PERMEABILITY AND IN SERUM LEVELS OF IgG AND ALBUMIN (fig 2)

A high CSF IgG/albumin ratio may merely reflect a high plasma level of IgG or, alternatively, a low

plasma albumin level. To correct for variations in the plasma levels of these patients a refinement in the CSF IgG/albumin quotient was used. This was the quotient CSF IgG/serum IgG (expressed as a percentage of the CSF/serum albumin ratio). The aim in using this quotient was to see if a better discrimination could be obtained between a neurological control group and a group of patients with MS. The relationship between this quotient and the quotients IgG/albumin and IgG/total protein is shown in fig 2, together with the proportion of values in the MS group which were above the $M + 2SD$ of the corresponding quotient in the other neurological disease group. All three groups have been subdivided, depending on whether the CSF total protein was above or below 75 mg%. Thus it is seen in this figure that the upper limit for the neurological control group was higher if a breach in the blood/CSF barrier had occurred. Comparison of these three quotients shows that the proportion of MS patients with an elevated IgG/albumin or IgG/total protein quotient is less than that seen using the third quotient.

Fig 2 The comparison of three different quotients derived for the same group of 35 patients with multiple sclerosis (MS) when compared with 27 patients with other neurological diseases (OND). Each group has been subdivided into two, depending on whether the CSF total protein was normal (left bracket of each group) or greater than 75 mg% (right bracket of each group). In comparing the three different quotients, note the higher proportion of multiple sclerosis patients with an elevated CSF/serum IgG ÷ CSF/serum albumin quotient. This suggests that this latter quotient is more discriminating in distinguishing patients with multiple sclerosis from those with other neurological disorders.

KAPPA/LAMBDA RATIO (fig 3)

Recent evidence has shown a preferential increase in the kappa light chain subclass of CSF IgG in some patients with MS (Zettervall and Link, 1970). Consequently the CSF kappa/lambda ratio was measured for many of the patients in the present study.

The one grossly elevated value in the neurological control group was from the patient with dementia, who also had an elevated IgG/albumin quotient (*vide supra*).

An elevated κ/λ ratio was observed in 10/30 (33%) patients with definite MS and 10/38 (26%) patients with possible or probable MS when compared with the neurological control group.

Elevated κ/λ ratios were also seen in one patient with SSPE, two patients with HSVE, and one patient with tuberculous meningitis (fig 3).

With the exception of six MS patients, an elevated

κ/λ ratio was always associated with a raised IgG/albumin quotient (fig 4).

IGA/ALBUMIN QUOTIENT AND CSF IgM (fig 5 and table I)

The IgA/albumin quotient was of little value in distinguishing between the various diagnostic groups (fig 5). However, it was interesting to note that two patients with neurosyphilis, one with HSVE and one with a cerebral abscess, had elevated IgA/albumin quotients when compared with the neurological control group. (An upper limit for the IgA/albumin quotient was arbitrarily set at 5% in order to exclude the upper 2.5% of specimens of the neurological control group.) It was additionally noted that three other patients with HSVE had high normal values between 4% and 5%.

CSF IgM was measured in many of the patients,

Fig 3 The κ/λ ratios obtained for the various diagnostic groups.

including all those with MS or neurological infections. IgM was not measurable in the CSF of any patients with MS. Six patients with CNS infection had measurable CSF IgM. These consisted of four patients with HSVE, one with neurosyphilis, and one with tuberculous meningitis. Two patients with polyneuritis also had IgM in the CSF. The relationship between the CSF immunoglobulins and the total proteins for all these patients is shown in table I.

Assessment of viral antibodies and a comparison with the CSF immunoglobulin quotients

A number of CSF and serum specimens were tested for antibodies against three viruses. These results will now be described and a comparison made with the corresponding CSF IgG/albumin quotient and the kappa/lambda ratio.

ANTIBODY AGAINST MEASLES VIRUS

Thirty-two paired serum and CSF specimens from patients with MS or other neurological disorders and an additional 37 CSF specimens from MS patients and 10 from patients with other neurological disorders (all of these 47 latter specimens had elevated IgG/albumin quotients) were examined for measles antibody.

The histogram of the serum measles antibody titre is shown in figure 6. The median for the serum measles titre for the MS group was significantly higher than that for the other neurological disease group; 1:64 compared with 1:8; $0.02 < P < 0.05$ (Wilcoxon sum of ranks statistical test). Seven of these MS CSF specimens had measles antibody with a titre varying from 1:8 to 1:2 (fig 6). Three specimens in the other neurological disease group also had antibody but with titres less than 1:2. In

Patient	Age	Sex	Diagnosis	Cell count (mm ⁻³)	Total protein (mg %)	IgG/albumin %	CSF serum %	IgG/albumin	κ/λ	Viral antibody titre			
										Serum measles	CSF Measles	HSV	Mumps
1	31	M	Definite	8	104	16.4	97	2.04	1:128	1:4	—	—	—
2	28	M	Definite	10	42	18.9	74.4	1.5	1:64	1: < 2	—	—	—
3	21	F	Probable	8	58	23.9	90.6	2.08	1:128	1: < 2	—	—	—
4	23	F	Probable	8	51	15.1	39.7	1.12	1:64	1: < 2	—	—	—
5	39	F	Probable	5	56	19.4	ND	2.35	1:64	1: < 2	—	—	—
6	54	F	Probable	0	40	20.2	106	1.77	ND	1:16	—	ND	ND
7	63	M	Possible	ND	51	30.4	ND	1.21	ND	1:4	1: < 2	ND	ND
8	27	F	Definite	14	43	31.8	ND	1.38	ND	1:4/8	1: < 2	ND	ND
9	42	F	Probable	42	158	19.9	ND	1.69	ND	1:2	—	ND	ND
10	55	F	Definite	3	57.5	35	177	1.61	1:128	1:8	—	—	—
11	22	M	Definite	83	43	42.8	189	1.5	1:512	1:16	—	—	—

Table I Patients with MS in which measles antibody was detected in CSF

— negative; ND not done.

Fig 4 Scattergram of the CSF κ/λ ratio and the IgG/albumin quotient for 68 patients with MS. The dashed lines indicate the upper limit for the neurological control group. Note the six specimens with normal IgG/albumin quotients but with elevated κ/λ ratios.

general, patients with detectable CSF measles antibody also had high serum titres; this relationship and the mean age and sex ratio for both groups are shown in figure 6. The CSF total proteins were comparable in both groups.

From the 47 additional CSF specimens screened for measles antibody, four were found (all were from patients with MS) to contain antibody and

with a titre varying from 1:2 to 1:16. Two of these positive specimens also had antibody against HSV (titre 1: < 2), but in neither was the CSF total protein elevated, and both had only slightly elevated IgG/albumin quotients (table I).

The presence of CSF measles antibody in the MS group was variably related to an elevated IgG/albumin quotient. Seven patients out of the 53 tested had detectable measles antibody associated with normal values for the IgG/albumin whereas only four patients with antibody showed an elevated IgG/albumin quotient (table II). In particular, two patients had high CSF titres of measles antibody (1:16, 1:4) but normal IgG/albumin quotients. The serum measles titre was 1:128 in the second patient (it was not measured in the first) and the CSF total protein was normal in the first patient and elevated to 105 mg% in the second.

The single patient with SSPE had a grossly abnormal CSF/serum measles titre ratio of 1:8 and a CSF total protein of 84 mg%.

ANTIBODY AGAINST HERPES SIMPLEX VIRUS

The CSF and serum from all nine patients with HSVE and the CSF from 54 patients with MS and from 26 patients with other neurological disorders were tested for antibody against HSV.

Antibody against HSV was detected in the CSF in eight of the nine HSVE patients. In the antibody

Patient	Diagnosis	CSF total protein (mg %)	IgG/albumin %	IgA/albumin %	IgM (mg %)	κ/λ
1	HSVE	132	55.0	4.40	0.85	1.05
2	HSVE	175	66.1	4.04	0.10	1.51
3	HSVE	224	133.0	8.49	1.30	1.66
4	HSVE	319	17.3	1.53	0.13	1.51
5	Neurosyphilis	85	95.6	6.43	0.10	1.81
6	TB meningitis	367	18.6	3.0	3.0	1.64
7	Polyneuropathy	570	20.3	3.30	0.85	—
8	Polyneuropathy	330	18.4	1.58	0.13 s	1.3

Table II Patients with all three immunoglobulins detected in the CSF

Fig 5 *IgA/albumin quotients obtained for the various groups.*

Fig 6 *Relationship between serum and CSF titre of measles antibody for a group of patients with definite or suspected MS and for patients with other neurological disorders.*

positive patients the ratio of the CSF/serum antibody titres varied between 1:1 and 1:16, grossly abnormal values (MacCallum *et al*, 1974). These viral studies have been reported elsewhere and will

not be further discussed (MacCallum *et al*, 1974).

The IgG/albumin quotient was elevated in six of the antibody positive patients. In addition, two of the remaining three patients had high normal quotients of 27.5% and 25.6% (see fig 1). In the former patient an abnormal total protein of 109 mg% was recorded while in the other the total protein was normal. The CSF/serum antibody titre was 1:16 in the former patient and it was not measured in the latter.

No antibody against HSV was detected in any of the CSF specimens from the neurological control group while two patients with MS had antibody against HSV (*vide supra*).

One patient with neurosyphilis showed a CSF antibody titre to both HSV (1:16) and measles virus (1:4). The CSF protein in this patient was 85 mg% and 25% of this was IgG.

ANTIBODY AGAINST MUMPS VIRUS

The CSF from 17 patients with MS and from 16 patients with other neurological disorders was examined for mumps antibody. No antibody was detected in any of these specimens.

Discussion

The results of this study have confirmed the original observation of Kabat and his colleagues (1948) and subsequent workers that a relative rise in CSF IgG is frequently seen in demyelinating and infecting CNS disorders.

Link and Müller (1971), in a recent comprehensive study, noted a relative increase in CSF IgG in 73% of 64 patients with definite MS, in 36% of 39 patients with CNS infections, and in 16% of 81 patients with other neurological disorders when compared with 30 'healthy' controls. However, in clinical neurological practice it is often not so much a problem of distinguishing normal from abnormal but in distinguishing MS from non-MS or CNS infections from non-infections. We have, therefore, compared a group of patients with CNS infections, MS or polyneuritis with a group comprised of patients with other neurological disorders. The results of this study have shown that the measurement of the relative concentration of IgG in the CSF can be of diagnostic value and help in distinguishing MS and CNS infections from other neurological disorders.

It has also been shown that distribution of the values of the relative CSF IgG, as assessed by the IgG/albumin quotient, obtained for patients with radiologically proven cervical spondylosis or lumbar disc herniation was similar to that obtained for the larger neurological control group. If this smaller group is taken as a 'normal' group, representing the situation seen in healthy individuals, this latter finding suggests that a relative increase in CSF IgG is uncommon in neurological disorders apart from MS and CNS infections. This conclusion is supported by other investigators who have found that between 5.5% and 22% of patients with other neurological disorders show elevated values of CSF IgG quotients when compared with essentially healthy subjects (Kabat *et al*, 1950; Harter *et al*, 1962; Schneck and Claman, 1969; Riddoch and Thompson, 1970; Link and Müller, 1971). However, it is difficult to compare or contrast individual studies due to the different diagnostic criteria and CSF quotients used in the assessment of the patients.

In many studies a small number of patients with presenile dementia, with or without extrapyramidal features, have been noted to show elevations of the relative CSF IgG concentration (Yahr *et al*, 1954; Riddoch and Thompson, 1970; Link and Müller, 1971; Skrabanek *et al*, 1973). In the present study two such patients were observed. The clinical features of one patient were non-specific while the pathological examination of the CNS in the second showed only a cerebral infarct. In neither patient

was the serum examined for the presence of a polyclonal or monoclonal increase in IgG which would also increase the CSF IgG/albumin quotient (Riddoch and Thompson, 1970). It would be of interest to know whether such patients have undiagnosed MS, which occasionally gives rise to a presenile dementing process (McAlpine *et al*, 1972); a CNS infection such as HSV, which has been suggested to be a cause of early dementia (MacCallum, *et al*, 1974); or whether these patients suffer from another disorder.

The IgG/albumin quotient was elevated in 53% of the patients with definite MS as compared with 28% of the patients with suspected MS. The difference between these groups could be due to the inclusion of patients in the latter group who will ultimately turn out to have another disease. But, alternatively, since many of these suspected MS patients were suffering from an initial acute neurological episode, this might suggest that the IgG/albumin quotient is not elevated in the early stages of MS with the same frequency as is seen for established MS. Follow-up and serial estimations of the IgG/albumin quotient in these suspected MS patients will help to clarify this problem. However, Glasner (1974) has noted a rise in the relative CSF IgG concentration in the first few months after the initial attack in the majority of 96 patients with MS. The relative IgG concentration appeared to stabilize after an interval of one year from the initial episode.

One-third of the definite MS patients in this study had an elevated kappa/lambda ratio when compared with the neurological control group. This figure is a little lower than the 53% obtained by Link and Müller (1971). These investigators also measured the same ratio in the serum of their patients and found no difference between the groups. They therefore concluded that the increase in the kappa/lambda ratio in the MS CSF was probably due to a disproportionate increase in the quantity of the IgG molecules with light chain of type kappa. Why this should occur is not known.

Viral antibody studies were performed in many of the MS patients. The increased serum titre of measles antibody in a group of 16 patients with MS when compared with a group having other neurological disorders, is in accord with previously reported studies (Adams and Imagawa, 1962; Haire *et al*, 1973).

Norrby *et al* (1974) have studied measles titres in serum and CSF in 30 patients with definite MS and in 30 patients with other neurological disorders. They found haemagglutination-inhibiting and/or nucleocapsid complement-fixing measles antibody in 13 MS CSF specimens in contrast to their neurological control group in which only two specimens

were positive. They also found a significant reduction in the serum/CSF ratio of these measles antibodies in 12 of the 30 MS patients but did not see any reduction in their neurological disease group. These investigators conclude that antibody against measles virus is produced in the CNS of some MS patients.

In the present study the examination of 53 CSF specimens from patients with definite or suspected MS revealed antibody in 11. Seven of these antibody positive patients had a normal IgG/albumin quotient. In the study of Norrby *et al* (1974) four of their MS patients had a normal IgG/total protein quotient and one of these had a significantly reduced serum/CSF ratio of measles antibody. Both these findings therefore suggest that some patients with MS may have CNS production of measles antibody without any elevation of the relative concentration of CSF IgG. The assessment of CSF measles antibody or, more importantly, the serum/CSF measles antibody titre may be useful in detecting some patients with MS who have normal IgG/albumin quotients.

Rosenthal and Soothill (1962) have shown that the concentration of CSF IgG and albumin is dependent on the concentration of these proteins in the plasma. To account for variations in the levels of these plasma proteins the quotient CSF/serum IgG, expressed as a percentage of the CSF/serum albumin, was measured in MS and other neurological patients and compared with the IgG/albumin and IgG/total protein quotient. It was observed that an increased proportion of patients with definite or suspected MS had elevated values of this former quotient when compared with the latter two quotients. Furthermore, in two patients the IgG/albumin and IgG/total protein quotients were normal but were associated with an elevated CSF/serum quotient and with an abnormal κ/λ ratio and with detectable measles antibody in the CSF. These findings suggested that this latter quotient is more discriminating in detecting patients with MS than the more generally used IgG/albumin or IgG/total protein quotient.

It was of particular interest that 6/9 patients with herpetic encephalitis had marked elevations of the IgG/albumin quotient. These six specimens of CSF were all obtained between the 12th and the 200th day of the illness. Normal quotients were seen in one patient at the second day of the illness and in another who had survived for longer than one year. A rising quotient was also observed in one patient in the early stages of the disease and a falling quotient in another (over a five-month period). These observations are reminiscent of the rise seen in the CSF titre of antibody to HSV in the first two weeks of the

disease and the slow decline over the following months (MacCallum *et al*, 1974).

A similar increase in CSF IgG in HSVE has been previously noted by von Welsum and van der Helm (1970), Rappel *et al* (1971), and Link and Müller (1971), but only in the latter study have the CSF immunoglobulins been measured quantitatively.

Elevation of the IgG/albumin quotient was also found in the present study in cases of neurosyphilis SSPE, cerebral abscess, and meningitis, as has been previously described by others (Yahr *et al*, 1954; Link and Müller, 1971).

Patients with polyneuropathies, including those with the characteristic features of the Guillain-Barré syndrome, have been recorded in which a relative increase in the CSF IgG or gamma globulin has occurred (Harter *et al*, 1962; Laterre *et al*, 1970; Link, 1973). In general, the frequency of occurrence is low and compares with the 17% seen in the present study. The nature or cause of the selective increase of CSF IgG is unknown. Link (1973) has also described monoclonal bands occurring in the serum of 8 out of 10 patients with the Guillain-Barré syndrome similar to that seen for one patient in the present study. The origin and function of this monoclonal immunoglobulin are unknown.

The measurement of CSF IgA and IgM was not of great use in the comparison of the various groups. IgA and IgM were relatively increased in some patients with CNS infection but were too few in numbers in these groups for one to decide whether this was a constant feature. It appeared that IgA and IgM were not included in the CNS antibody response seen in MS, and this finding is in keeping with the conclusion of other investigators (Link, 1967; Link and Müller, 1971).

Five patients out of 16 tested with CNS infections showed an elevated CSF κ/λ ratio while 2/5 patients with polyneuropathy also showed this increase. This is in contrast to the findings of Link and Müller (1971) where none of the 39 patients with CNS infections showed any change in this ratio. The present results show that alterations in the κ/λ ratio are not specific for MS.

In conclusion, it is considered that the estimation of the relative concentration of CSF immunoglobulin, together with other methods of CSF immunoglobulin analysis (including κ/λ ratio, viral antibody studies, and electrophoresis), will supplement each other in the endeavour to detect pathological production of immunoglobulin in the CNS in certain neurological conditions.

We should like to thank the consultants and staff of the Neurology Department, Churchill Hospital for allowing us to study their patients. PJR-T is a re-

cipient of the Senior Hulme (Overseas) Scholarship, Brasenose College, Oxford. Mrs A. Houghton gave much appreciated secretarial assistance.

We gratefully acknowledge the generosity of Dr F. O. MacCallum in contributing seven specimens of CSF from patients with HSVE, and his staff for measuring the viral antibody titres.

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