Arch Psychiatr Nervenkr (1983) 233 : 253–262

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Protein Pattern of Cerebrospinal Fluid in Various Neurological Diseases

C. R. Hornig, O. Busse, and W. Dorndorf

Department of Neurology, Justus Liebig University, Am Steg 14, D-6300 Gießen, Federal Republic of Germany

Summary. CSF/serum albumin and immunoglobulin G ratios were determined in 520 patients suffering from various neurological diseases. Blood-brain barrier impairment was detectable in most cases of spinal tumour, meningitis, Guillain-Barré syndrome and in two-thirds of the patients with cerebral infarctions. A local IgG formation in the CNS has to be assumed for some cases of meningitis considering the course of the protein dysequilibrium. Autochthonous IgG production together with a barrier dysfunction was found in patients with encephalitis, meningoradiculitis and neurosyphilis. In cases of multiple sclerosis local IgG formation in the CNS was the predominant finding.

Key words: Cerebrospinal fluid – Blood-brain barrier – Immunoglobulin G – CSF protein profile

Zusammenfassung. Die Liquor/Serum-Konzentrationsquotienten für Albumin und Immunglobulin G wurden bei 520 Patienten mit unterschiedlichen neurologischen Erkrankungen bestimmt. Eine Störung der Blut-Liquor Schranke hatten die meisten Patienten mit spinalen Tumoren, Meningitiden, Polyradiculitiden und zwei Drittel der Fälle mit Hirninfarkten. Eine lokale IgG-Synthese im Zentralnervensystem muß für einen Teil der Patienten mit Meningitiden angenommen werden. Eine autochthone IgG Bildung zusammen mit einer Blut-Liquorschrankenstörung fanden wir bei Enzephalitiden, Meningoradiculitiden und der Lues cerebrospinalis. Die lokale IgG Produktion war der vorherrschende Befund bei der multiplen Sklerose.

Schlüsselwörter: Liquor cerebrospinalis – Blut-Hirn-Schranke – Immunglobulin G – Liquor-Protein-Profil

Introduction

Quantitative determination of certain cerebrospinal fluid (CSF) proteins, namely albumin and immunoglobulin G (IgG) should be part of routine liquor examina-

Offprint requests to: W. Dorndorf at the above address

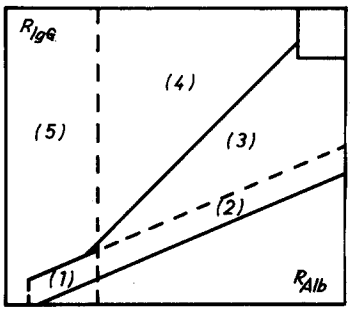

Fig. 1. Diagram for the evaluation of the CSF protein profile. Interpretation: *(1)* normal range, *(2)* BBB dysfunction with proportionally increased R_{alb} and R_{IgG}, *(3)* BBB dysfunction with disproportionally increased R_{IgG}, autochthonus IgG formation possible, *(4)* BBB dysfunction with additionally autochthonus IgG formation, *(5)* normal BBB function with autochtonus IgG formation

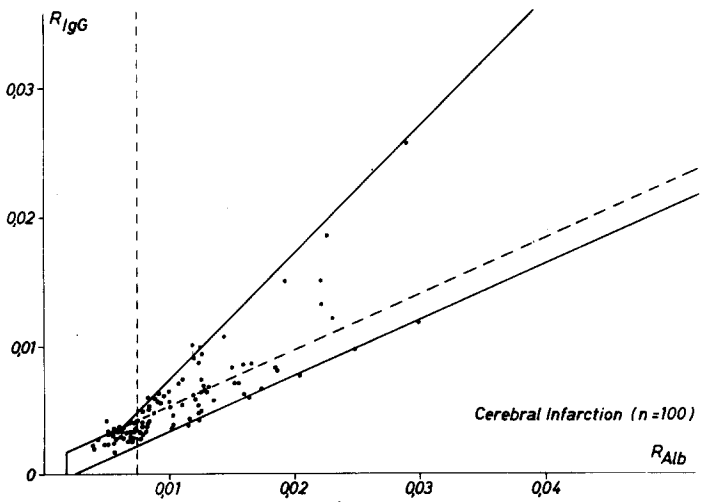

Fig. 2. CSF protein profile of patients suffering from cerebral infarction

tions. Modern diagnostic tools such as the radial immunodiffusion technique, laser nephelometry and turbidimetry make rapid, simple and reliable measurements possible. Considering the dependency of albumin and IgG concentrations in CSF on the serum concentrations the use of CSF/serum ratios is of great value (Ganrot and Laurell 1974). The use of evaluation diagrams has proved helpful in the interpretation of results (Schliep and Felgenhauer 1978; Reiber 1980). In this report findings of protein patterns in various neurological diseases are described.

Materials and Methods

Albumin and IgG concentrations were determined in lumbar CSF and serum of 520 patients suffering from various neurological diseases. Usually one lumbar puncture was performed on the day of hospital admission, though in some cases more than one lumbar puncture was carried out. Albumin and IgG were determined using a radial immunodiffusion technique (Tri-Partigenplatten, Behringwerke Marburg, FRG). The CSF/serum ratios (R_{alb} and R_{IgG}) were calculated and plotted into a diagram as described by Reiber (1980). For interpretation of the different regions of this diagram see Fig. 1.

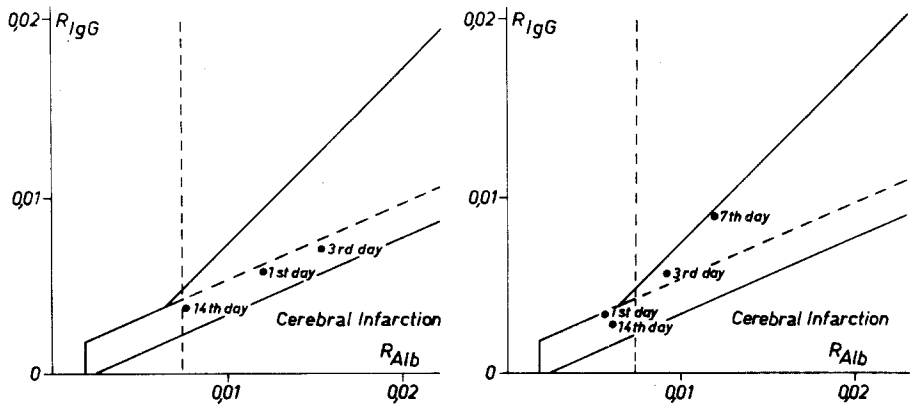

Fig. 3. Changes in a pathological CSF protein profile in the course of the disease. Two patients suffering from cerebral infarction

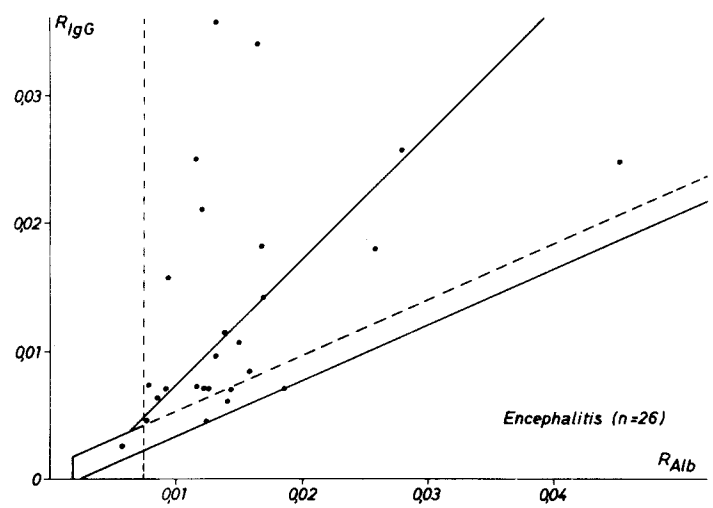

Fig. 4. CSF protein profile of patients suffering from viral encephalitis

Results

Cerebral Infarction. A blood-brain barrier (BBB) disturbance was observed in 68 out of 100 patients, and 37% of these patients afforded a moderate proportionate type of barrier dysfunction. In only 8 cases did R_{alb} exceed a value of 0.02 (Fig. 2). From the results of 2 patients, who had several lumbar punctures at different times after stroke, it was concluded that BBB dysfunction reaches its maximum several days after the onset of symptoms (Fig. 3).

Encephalitis. Of the 26 patients suffering from viral encephalitis 96% had a moderately disturbed BBB. In only 3 cases was the R_{alb} value about 0.02. A local IgG synthesis was ascertained in 46% of cases and it was considered as possible in a further 35% (Fig. 4).

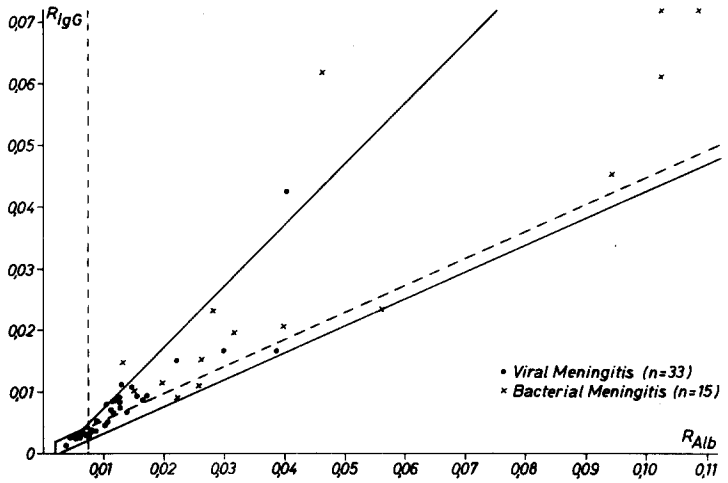

Fig. 5. CSF protein profile of patients suffering from meningitis of bacterial or viral etiology

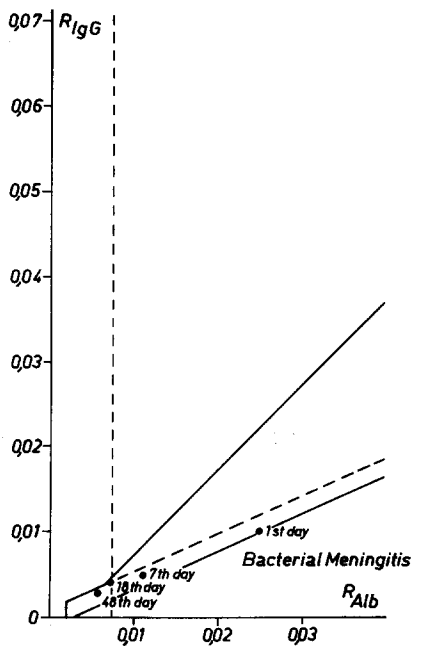

Fig. 6. Changes in a pathological CSF protein profile in the course of the disease. A patient suffering from bacterial meningitis

Meningitis. We examined 33 cases of viral, 15 cases of bacterial and 7 cases of tuberculous etiology and our findings are illustrated in Fig. 5. Whereas one-fourth of the patients suffering from viral meningitis had a normal barrier function, it was disturbed in all cases of bacterial and tuberculous meningitis. While BBB impairment was mild or moderate in viral meningitis with a mean R_{alb} of 0.013, it was more extensive in bacterial meningitis with a mean R_{alb} of 0.051 and in tuberculous meningitis with a mean R_{alb} of even 0.075. An autochthonous IgG

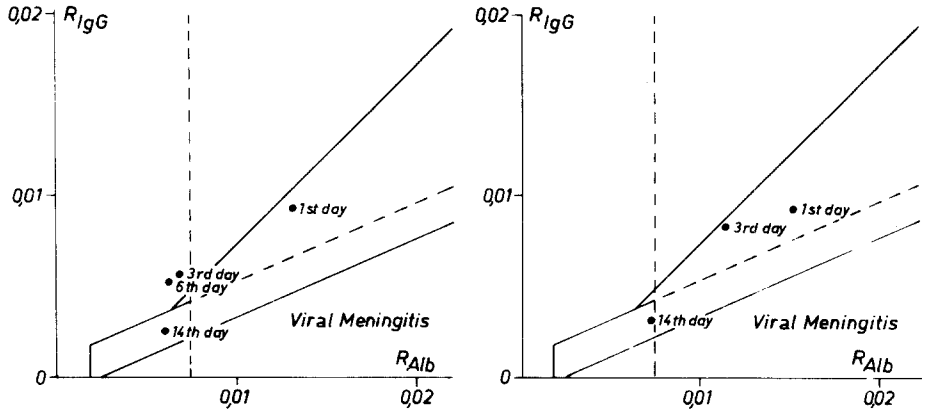

Fig. 7. Changes in a pathological CSF protein profile in the course of the disease. Two patients suffering from viral meningitis

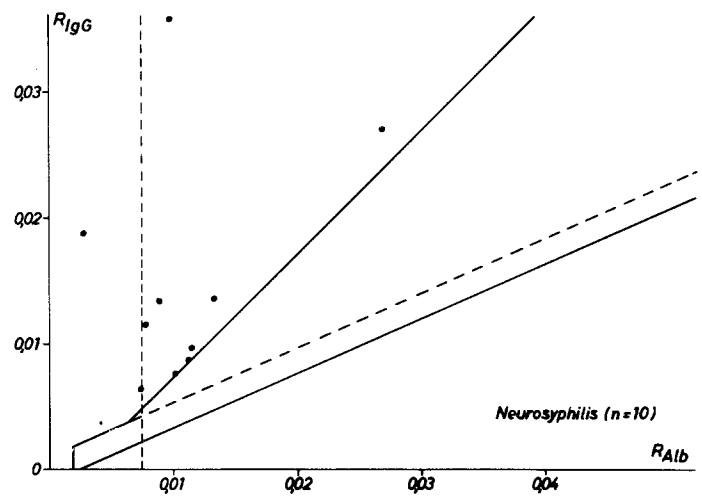

Fig. 8. CSF protein profile of patients suffering from neurosyphilis

formation in CNS was ascertained in 9% of viral, 13% of bacterial, and 43% of tuberculous meningitis cases. The rest of the latter were located in range (3) of the diagram, whereas 25% of the patients suffering from viral and 20% of those with bacterial meningitis only showed a proportionate barrier dysfunction.

Lumbar puncture was conducted more than once in 14 patients, and BBB disturbance in 4 cases of viral meningitis lasted no longer than 3 days and between 1 and 2 weeks in 4 other cases. In 4 patients suffering from bacterial meningitis a barrier impairment was detectable for approximately 14 days, though in 1 patient the impairment was detectable for 2 months. The 2 cases of tuberculous meningitis had a BBB dysfunction which lasted approximately 1 and 3 months respectively. Figures 6 and 7 show the protein profiles of 1 patient with a proportionate BBB disturbance caused by a bacterial meningitis, and 2 patients

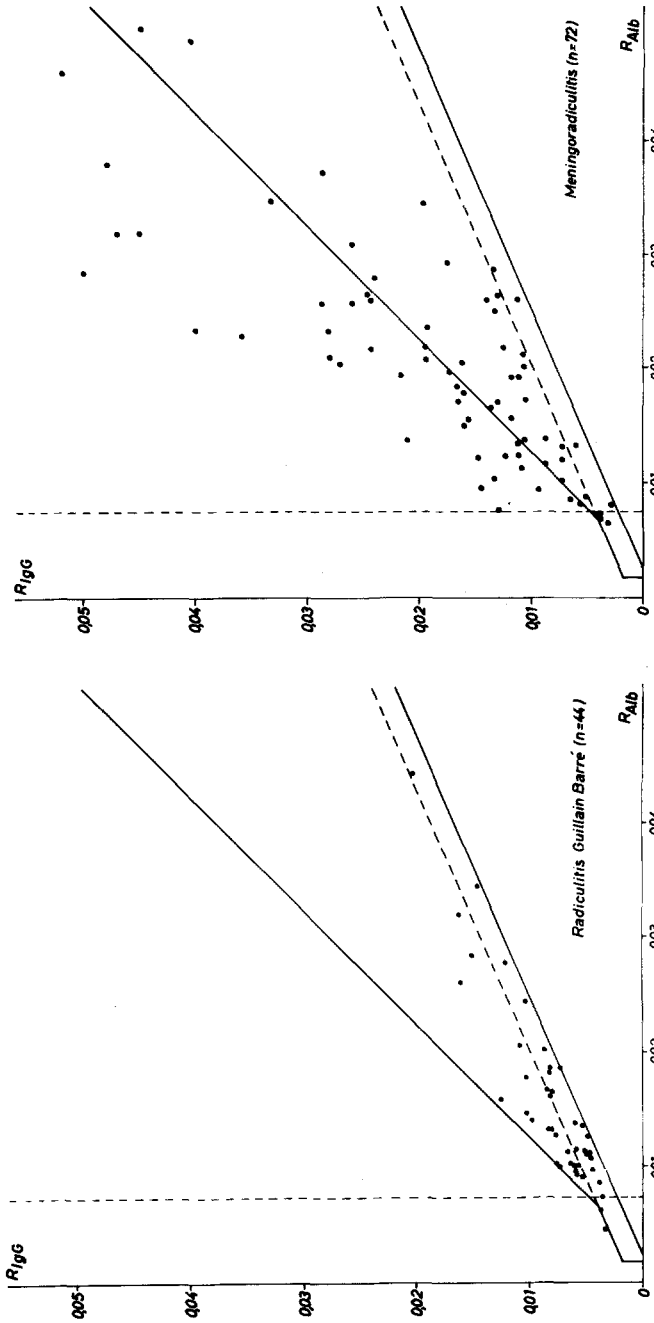

Fig. 9. CSF protein profile of patients suffering from Guillain-Barré syndrome and meningoradiculitis

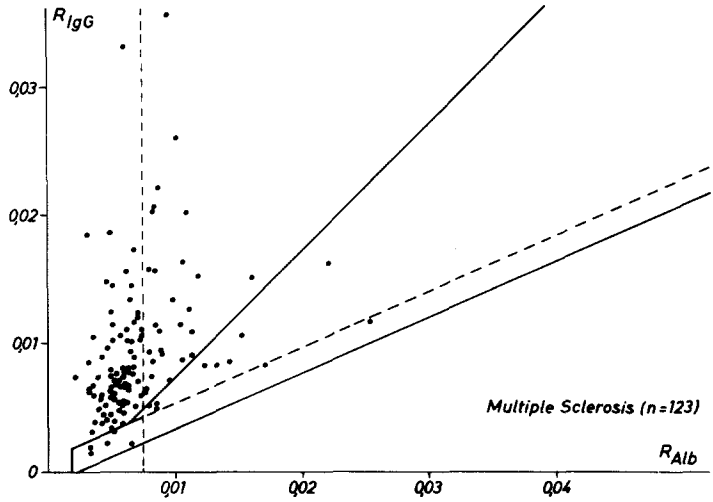

Fig. 10. CSF protein profile of patients suffering from multiple sclerosis

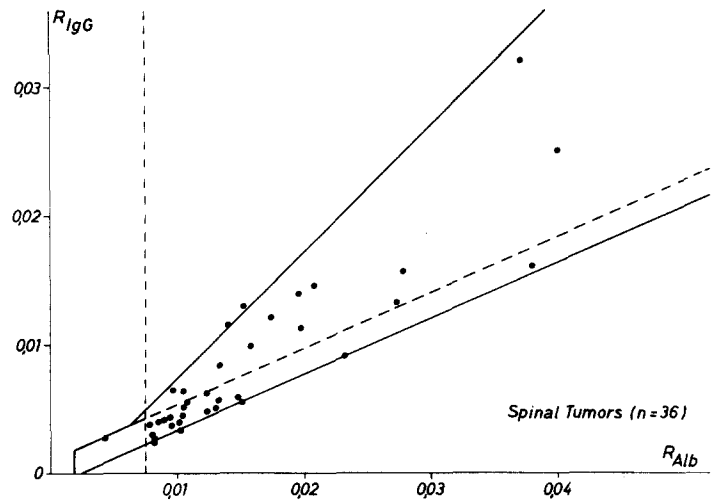

Fig. 11. CSF protein profile of patients suffering from spinal tumours

suffering from viral meningitis over a period of time. In 1 patient there was an autochthonous IgG formation during the course of the disease. Unfortunately, reestablishment of the BBB failed to develop continuously in all cases.

Neurosyphilis. None of the 10 patients suffering from neurosyphilis had a normal protein profile, and 8 patients had a BBB impairment of moderate degree with a mean R_{alb} of 0.013. In all 10 cases a certain local IgG production was observed (Fig. 8).

Guillain-Barré Syndrome. Of the patients suffering from this disease 96% had a disturbed barrier function. A distinction between the patients with Guillain-

Barré syndrome and those suffering from a meningoradiculitis (CSF pleocytosis exceeding 60/3 cells/mm^3) concerning frequency and extension of the barrier impairment was not apparent. The mean R_{alb} value was 0.016 for patients with Guillain-Barré syndrome and 0.02 for those suffering from meningoradiculitis. On the other hand, the two groups differed in the R_{IgG} values. Of the patients with Guillain-Barré syndrome 50% had a proportionate barrier disturbance only and a further 45% had to be plotted into range (3) of the diagram. Of the meningoradiculitis patients 51% had a certain and a further 39% a possible autochthonous IgG formation within the CNS (Fig. 9).

Multiple Sclerosis. Of the 123 patients suffering from multiple sclerosis 30% had a barrier impairment of mostly mild or moderate degree. Local IgG production in the CNS was observed in 88% of these patients and 22% showed an additional barrier dysfunction. The protein profile was normal in 4% and barrier impairment alone was observed in only 2% of the multiple sclerosis patients (Fig. 10).

Spinal Tumours. Of 36 patients suffering from different spinal space occupying processes only 1 had a normal protein profile. In 2 cases a weak local IgG formation was observed. Most patients, namely 58%, had a proportionate and a further 39% a disproportionate barrier dysfunction. The impairment was mostly of a moderate degree with a mean R_{alb} of 0.015 (Fig. 11).

Discussion

Nearly 70% of the patients suffering from cerebral infarction had a BBB impairment of a moderate degree. Our results indicated that the maximum BBB damage occurred a few days after stroke. It coincided with the maximum infarction edema in cranial computed tomography (CT), and therefore a relation to prognosis has to be assumed (Busse 1982).

Alterations in the CSF protein pattern of patients suffering from encephalitis were characterized by a BBB dysfunction in nearly all cases and an additional autochthonous IgG synthesis in one-half of them. The R_{IgG} values in some cases reached very high levels, which probably reflected the expression of the humoral immune response within the CNS. It seemed to be more pronounced whenever the nervous tissue itself was involved in the inflammatory process as compared to a meningitis alone. Chronic inflammatory processes of nervous tissue such as neurosyphilis nearly always resulted in a distinct local IgG formation.

Only 3 patients suffering from meningitis of nontuberculous etiology had a proven autochthonous IgG production. In most other cases a minimal or moderate IgG formation was not detectable due to the additional BBB disturbance (Ganrot-Norlin 1978). But as the R_{IgG} values increased within the first days of the course of viral meningitis for example, an autochthonous IgG synthesis should be assumed to occur in the subacute phase of the disease although demonstration of this has failed in most cases (Schliep and Felgenhauer 1978). Nevertheless, a marked local IgG synthesis was found in tuberculous meningitis, which was probably caused by the following two factors: firstly tubercolous meningitis is a more chronic inflammation, and secondly it is often associated with tuber-

culomas within the CNS, representing a potential stimulus for antibody formation. Impairment of the BBB was more pronounced in bacterial than in viral meningitis since R_{alb} values reached the highest levels in cases of tuberculous meningitis, which may be of some importance in differential diagnosis.

Nearly all of the patients suffering from meningoradiculitis or Guillain-Barré syndrome showed evidence of an impaired barrier function. The two groups did not differ significantly in this respect. Although in approximately 50% of the patients with meningoradiculitis an autochthonous IgG formation was clearly present, it could be excluded in 50% of those patients with Guillain-Barré syndrome. For the remaining patients the findings were inconclusive. This observation is in agreement with the results of Link et al. (1979) who found oligoclonal IgG in only 1 of 11 cases suffering from Guillain-Barré syndrome with a normal CSF cell count, but in 9 of 13 cases with a CSF pleocytosis.

In the sera of most Guillain-Barré syndrome patients humoral antibodies against peripheral nervous tissue are detectable (Lisak et al. 1975; Vedelar et al. 1982) and in some cases additional antibodies against myelin of the CNS are present (Cook et al. 1971; Nyland and Aarli 1978). The same distinction is observed concerning cell mediated immunity (Abramsky et al. 1975). Involvement of the CNS in the inflammatory process is discussed for the group with immune reactions to peripheral as well as to central nervous tissue. As a local immune response within the CNS can be expected in those cases, the frequent autochthonous IgG formation with patients suffering from a meningoradiculitis becomes understandable, as CSF pleocytosis may be an expression of the inflammation of the CNS.

Of the patients suffering from multiple sclerosis 88% had a certain autochthonous IgG formation in the CNS, and it was considered as possible in a further 8%. In those cases, determination of oligoclonal IgG would have proved the assumption (Delmotte 1971). As local IgG synthesis can be found in such a large percentage of multiple sclerosis patients diagnosis should be questioned if demonstration of autochthonus IgG fails. Of our multiple sclerosis patients 30% had a mild or moderate barrier disturbance. This is in good agreement with the results of others (Eickhoff et al. 1977). In CT an enhancement of contrast medium can often be seen in demyelinated plaques within the CNS of multiple sclerosis patients (Sears et al. 1982). As contrast enhancement in CT may be an expression of a disturbed BBB, those plaques may be one source of an increased albumin level in the CSF.

Impediment of CSF flow in the spinal canal by a space occupying process results in a mostly proportionated increase of CSF protein concentration (Felgenhauer et al. 1976). Certain tumours, such as an epidermoid, can seldom act as a stimulus for local antibody formation (Sayk 1981).

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Received January 18, 1983