Eur Arch Psychiatr Neurol Sci (1987) 236:257–259

European Archives of Psychiatry and Neurological Sciences

Blood-Cerebrospinal Fluid Barrier in Schizophrenic Patients

Kurt Bauer and Johannes Kornhuber

Department of Neurology, University of Ulm, Steinhövelstrasse 9, D-7900 Ulm, Federal Republic of Germany

Summary. A total of 15 young white male patients newly diagnosed as schizophrenic (DMS III) were examined for signs of blood-cerebrospinal fluid (CSF) barrier alteration and CNS IgG synthesis. Of the 15 patients, 8 exhibited signs of increased blood-CSF barrier permeability. There was a high correlation between the ratio for CSF/serum albumin concentration and the CSF total protein concentration. Local IgG synthesis in the CNS was not detected in any of the patients.

Key words: Schizophrenia – Blood-cerebrospinal fluid barrier – Albumin – IgG – Total cerebrospinal fluid protein

Introduction

Increased total protein concentration in the cerebrospinal fluid (CSF) of schizophrenics was first reported over 50 years ago (Kafka and Samson 1928; Kopp 1934; Solomon et al. 1940; Bruetsch et al. 1942; Meyer 1949; Demme 1950; Habeck 1959; Hunter et al. 1969; but see also Oxenstierna et al. 1984; Ahokas et al. 1985). More recent studies have confirmed that total protein concentration in the CSF of psychotic patients is increased, and have related this finding to the observation that permeability of the blood-CSF barrier may be increased in these patients. A detailed study of changes in blood-CSF barrier in paranoid psychotic patients has been published by Axelsson et al. (1982), who found enhanced permeability in 7 out of 25 patients. Torrey et al. (1985) reported an abnormal blood-CSF barrier in only 4 out of 58 schizophrenic or schizoaffective patients, and Kirch et al. (1985) reported changes in the blood-CSF barrier in 7 of 24 chronic schizophrenics. Since differences in duration of illness, subdiagnosis, age and genetic characteristics may partially account for the variability of these results, we have examined the CSF/serum albumin and IgG ratio in a more homogeneous group of patients. A preliminary communication has been published elsewhere (Kornhuber and Bauer 1986).

Methods

The patients were investigated at the Department of Neurology and Psychiatry of the Bundeswehrkrankenhaus Ulm between March 1985 and November 1986. Only patients newly diagnosed as schizophrenic were included in the study. The group consisted of 15 white male patients (mean age 23.6 years, range 19–37 years), diagnosed according to DMS III (Spitzer 1980). Five patients had no history of neuroleptic medication. Most of the other patients had received neuroleptic drugs for the first time 1 or 2 weeks before lumbar puncture. None of the patients had experienced electroconvulsive treatment. Every patient was thoroughly examined clinically and additional computed tomographic brain scans, skull X-rays, electroencephalograms, spinal taps and routine laboratory tests were performed. Syphilis was ruled out and both serum and CSF from 11 patients were tested for antibodies to common neurotropic viruses (rubella, measles, mumps, enterovirus pool, lymphocytic choriomeningitis, herpes hominis I/II, varicella zoster, Russian spring summer encephalitis, central European encephalitis). There were no signs of infection (body temperature, erythrocyte sedimentation rate, CSF cell count, antibodies to neurotropic viruses) or other known organic CNS diseases, such as neoplasm. None of the patients had a history of drug or alcohol abuse.

CSF was sampled by standard lumbar puncture in the sitting position. Samples of 10 ml were withdrawn and only clear, colourless samples were used. Blood samples from the antecubital vein were obtained at the same time.

CSF total protein was measured turbidimetrically after trichloroacetic acid precipitation. Concentrations of albumin and IgG were determined by an immunonephelometric method using a Beckman nephelometer. The exclusive synthesis of albumin in the liver (Frick and Scheid-Seydel 1958; Cutler et al. 1967) allows the CSF/serum albumin concentration ratio to be used as an indicator of permeability of the blood-CSF barrier (Tibbling et al. 1977; Reiber 1986). The relative permeability of the blood-CSF barrier was assessed by comparing the measured CSF/serum albumin ratios with the age-dependent reference values above the 2 SD limit of Tibbling et al. (1977) and Reiber (1986). Local CNS IgG synthesis was determined graphically according to the method of Reiber (1979, 1986) and also by the IgG index of Tibbling et al. (1977).

Results

The CSF/serum albumin ratios of the 15 schizophrenic patients are shown in Fig. 1. According to the different reference values of Tibbling et al. (1977) and Reiber (1986), 5 and 8 respectively of the 15 patients had significantly increased CSF/serum albumin ratios, and 7 patients were normal by both methods. Within both the normal and abnormal groups there was no apparent relationship between CSF/serum albumin ratio and neuroleptic treatment (Fig. 1). Figure 2 demonstrates the expected high correlation between CSF/serum albumin ratio and

Offprint requests to: J. Kornhuber's present address: Department of Psychiatry, University of Würzburg, Füchsleinstrasse 15, D-8700 Würzburg, Federal Republic of Germany

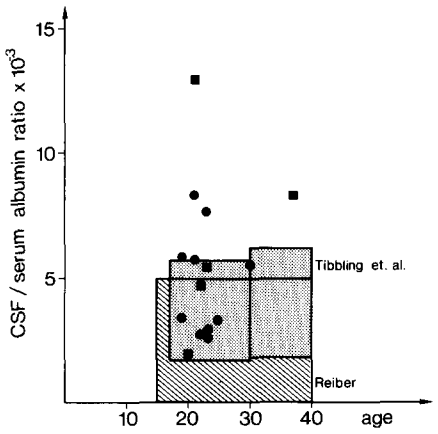

Fig. 1. Age and CSF/serum albumin ratio for 15 schizophrenic patients. Upper and lower limits (± 2 SD) of the age-dependent reference values according to Tibbling et al. (1977) and Reiber (1986) are indicated. Depending on the reference value, 5 and 8 out of 15 patients had enhanced blood-CSF barrier permeability. (■) patients without any history of neuroleptic medication. (●) patients receiving neuroleptic medication

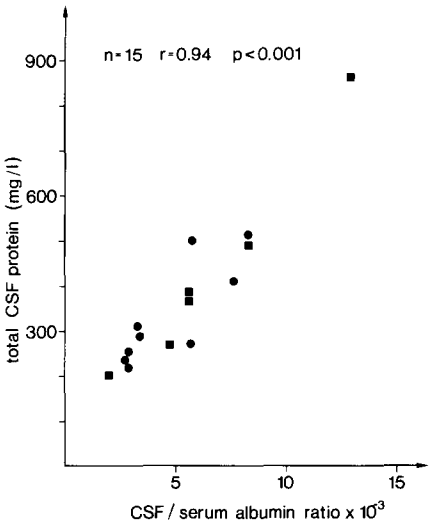

Fig. 2. Correlation between CSF/serum albumin ratio and CSF total protein in 15 schizophrenic patients. (■) patients without any history of neuroleptic medication. (●) patients receiving neuroleptic medication

CSF total protein ($r = 0.94$, $P < 0.001$). CSF IgG levels were elevated in only 1 patient. This patient had a high CSF IgG concentration (57 mg/l: reference values up to 40 mg/l) correlated with a markedly increased permeability of the blood-CSF barrier (CSF/serum albumin ratio: 12.9×10^{-3}). According to both the IgG index of Tibbling et al. (1977) and the evaluation graph of Reiber (1977, 1986) there was no local IgG production in the CNS in any patient (data not shown).

Discussion

The major result of our study was to confirm that permeability of the blood-CSF barrier was increased in a significant portion of a homogenous group of schizophrenics prior to prolonged treatment with neuroleptics. Our assessment of increased permeability was based upon comparison with two previously published reference values for the ratio of CSF-serum albumin concentration. Our study did not address the accuracy or reliability of these values. These reference values have been obtained only from neurological patients (Tibbling et al. 1977; Reiber 1979, 1986) suffering from clinically treated disorders such as dizziness and headache (Tibbling et al. 1977). Similar control values for the CSF/serum albumin ratio from healthy volunteers are not yet available. If the reference values of Tibbling et al. (1977) are used, our results are comparable with earlier reports (Axelsson et al. 1982; Kirch et al. 1985). The higher incidence of increased blood-CSF barrier permeability reported in these studies compared with the findings of Torrey et al. (1985) might be due to racial characteristics (88% of their patients were black). At present it is not known whether racial differences in blood-CSF barrier exist.

The observed high correlation between blood-CSF barrier permeability (i.e. the CSF/serum albumin ratio) and CSF total protein was expected since 2/3 of total CSF protein consists of albumin transported via plasma from the liver. These observations substantiate reports of earlier workers on CSF total protein in psychiatric patients (Kafka and Samson 1928; Kopp 1934; Solomon et al. 1940; Bruetsch et al. 1942; Meyer 1949; Demme 1950; Habeck 1959; Hunter et al. 1969).

The CSF/serum albumin ratio is widely accepted as a measure of the permeability of the barrier between blood and CSF. However, several factors other than blood-CSF barrier permeability are also known to influence this ratio. First, the function of the ventricular choroid plexus, which determines the CSF composition to a large extent, is under complex nervous control (Lindvall et al. 1977, 1978) and may be abnormal in schizophrenic patients. Second, recent studies have indicated that CSF circulation is impaired in schizophrenics (Oxenstierna et al. 1984). This observation may be important since there is an albumin concentration gradient along the neuraxis (Cutler et al. 1970; Weisner and Bernhardt 1978) and the CSF/serum albumin ratio measured using samples from lumbar punctures is a function of CSF turnover and circulation. The contribution of additional factors other than altered blood-CSF barrier permeability cannot be ruled out at this time.

Recent studies have concentrated on indications for viral infection or altered immunological function in schizophrenia (Torrey et al. 1978; Kaufmann et al. 1983; Knight 1984; Crow et al. 1986; Mendlewicz and Sevy 1986). In our study we found no intra blood-brain barrier IgG synthesis in schizophrenic patients. This is in agreement with Roos et al. (1985), but not with others (Torrey et al. 1978; DeLisi et al. 1981; Kirch et al. 1985).

In summary, our results confirm that CSF/serum albumin ratios indicative of increased blood-CSF barrier permeability are indeed observed in a homogenous group of schizophrenic patients prior to prolonged neuroleptic treatment. The various interpretations of this observation make it difficult to estimate its potential utility as a diagnostic tool or to subclassify schizophrenic disorders. To make better use of this information more basic data concerning barrier function in normals and other psychiatric patients is needed.

Acknowledgement. We would like to thank J. Kriebel, head of the Department of Neurology and Psychiatry at the Bundeswehrkrankenhaus Ulm, for valuable advice and generous support.

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Received June 30, 1986