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ORIGINAL ARTICLE

Signs of impaired blood-brain barrier function and lower IgG synthesis within the central nervous system in patients with schizophrenia or related psychosis, compared to that in controls

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Abstract

OBJECTIVES: Evidence has accumulated that an inflammatory, possibly autoimmune-mediated, process in the central nervous system (CNS), and by way of an aberrant immune system, may underlie the development of schizophrenia. Therefore, the aim of this study was to evaluate patients with schizophrenia or related psychosis for blood-brain barrier (BBB) function and immunoglobulin (Ig)G synthesis within the CNS.

METHODS: Fifteen patients with schizophrenia or schizoaffective disorder and 12 controls were investigated using lumbar puncture and blood sampling. Cerebrospinal fluid (CSF) and serum/plasma (S/P) were analysed for albumin and IgG by standard laboratory methods, and the ratio of CSF-albumin to P-albumin (marker of BBB function) and the IgG index (marker of CNS IgG synthesis) were calculated. Additionally, the patients were assessed for clinical symptoms with the Positive and Negative Syndrome Scale for schizophrenia.

RESULTS: The ratio of CSF-albumin to P-albumin was higher and the IgG index was lower in patients than in controls (p=0.045 and p=0.001, respectively). Moreover, subgroup analyses showed that patients in partial symptom remission had higher ratios of CSF-albumin to P-albumin than patients in full symptom remission, and that patients with heredity for schizophrenia or related psychosis had lower IgG indices than patients without heredity.

CONCLUSIONS: In this study we show that patients with schizophrenia or related psychosis have impaired BBB function and lower IgG synthesis within the CNS, compared to controls. These findings support the view that a pathological process within the CNS, combined with an aberrant immune system, may underlie the development of schizophrenia.

INTRODUCTION

Schizophrenia is a psychotic disorder that affects approximately 0.5% of the population worldwide (McGrath *et al.* 2008). It is in general disabling with a chronic course, beginning in late adolescence or early adulthood and continuing throughout life (Freedman 2003). The cause of schizophrenia is, in the main, still unknown. Nevertheless, the literature provides strong evidence for a role of genetic factors in its aetiology (Giegling *et al.* 2017; Li *et al.* 2017; Ptacek *et al.* 2011; Ripke *et al.* 2014). There are also indications that schizophrenia is a systemic disorder and not only a brain disease (Flyckt 2001; Kirkpatrick *et al.* 2014) and that somatic comorbidity in schizophrenia is relative common (Leucht *et al.* 2007; Melkersson & Wernroth 2017; Meltzer 1976; Mukherjee *et al.* 1996; Nasrallah 2005; Sørensen *et al.* 2015).

Over the years, evidence has also accumulated indicating that an inflammatory, possibly autoimmune-mediated, process in the central nervous system (CNS), combined with an aberrant immune system, may underlie the development of schizophrenia, at least in a subgroup of patients (Al-Diwani *et al.* 2017; Benros *et al.* 2011; Bergink *et al.* 2014; Braun *et al.* 2017; Ermakov *et al.* 2017; Horváth & Mirnics 2014; Laskaris *et al.* 2016; Miller *et al.* 2011; Müller *et al.* 2000; Trépanier *et al.* 2016; Upthegrove *et al.* 2014). Further, some studies have reported presence of micrometer-sized spherical particles and alterations in albumin- and immunoglobulin (Ig)G concentrations in cerebrospinal fluid (CSF) of patients with schizophrenia (Bechter *et al.* 2010; Johansson *et al.* 2012; Kirch *et al.* 1985, 1992; Mobarrez *et al.* 2013; Müller & Ackenheil 1995; Wetterberg *et al.* 2002); and in serum (S) of patients with schizophrenia, autoantibodies directed against brain tissue and blood cells have been detected (Abramson 1967; Kagami *et al.* 1987; Popova 1977; Shinitzky *et al.* 1991; Spivak *et al.* 2009a, 2009b).

Synthesis of albumin within the CNS has not been proven to occur and thus albumin present in CSF can be assumed to derive from S (Cutler *et al.* 1967; Tibbling *et al.* 1977). Therefore, the ratio of CSF-albumin to S/plasma (P)-albumin may be anticipated to be a more sensitive and better parameter for evaluating the blood-brain barrier (BBB) function than the CSF-albumin level alone (Link & Tibbling 1977a). In analogy with albumin, IgG penetrates from S to CSF, but in contrast to albumin, simultaneous synthesis of IgG within the CNS has been proven to occur (Link & Tibbling 1977b). It is also important to realize that S/P-albumin as well as S-IgG have a direct influence on the concentration of the corresponding protein in CSF, and an elevation of S/P-albumin or S-IgG above the upper limit of normal range will be accompanied by an increase in CSF of respective protein and vice versa (Tibbling *et al.* 1977). Then the CSF-albumin: S/P-albumin ratio, as well as the CSF-IgG: S-IgG ratio should be fairly constant when the serum concentrations change, and conversely, in the presence of impaired BBB function, each ratio should increase (Tibbling *et al.* 1977). The quotient between these two ratios, however, is expected to remain constant and of the same magnitude as in the subjects with a normal BBB (Tibbling *et al.* 1977). Therefore, this quotient designated the IgG index is expected to reflect the IgG synthesis within the CNS (Link & Tibbling 1977a, 1977b).

In this study, we evaluated patients with schizophrenia or related psychosis in partial or full symptom remission for BBB function by the CSF-albumin: P-albumin ratio, and for IgG synthesis within the CNS by the IgG index, and compared with control subjects.

MATERIAL AND METHODS

Ethical approval

The study was approved by The Ethics Committee of Karolinska Institutet and The Regional Ethical Review Board, Stockholm, Sweden, and all patients and control subjects participated after giving informed consent.

Patients & control subjects

Consecutive outpatients at psychiatric polyclinics in the region of Stockholm, Sweden, diagnosed with schizophrenia or schizoaffective disorder according to the DSM-5 criteria (American Psychiatric Association 2013), were invited to participate in this study. Any patients having a substance-related disorder, or a physical illness that could influence the evaluation were excluded. In total, 15 patients (7 men and 8 women) were included. Additionally, 12 sex- and age-matched individuals diagnosed with non-inflammatory neurological diseases were included as control subjects.

Characteristics of the patients and control subjects are given in *Table 1*. All patients were Caucasians and had a diagnosis of schizophrenia, except one woman who was diagnosed with schizoaffective disorder. Ten (66.7%) of the patients had heredity for schizophrenia or related psychosis, i.e. they had one or more first-, second-, third-, or fourth-degree relatives, siblings included, with such a disorder (Melkersson 2009; *Table 1*). None of the male patients compared to five (62.5%) of the female patients were smokers ($p = 0.026$), otherwise no sex differences in characteristics were found among the patients (*Table 1*). In addition, male and female patients were treated with similar antipsychotics (*Table 1*), and the only concomitant medications used were benzodiazepine derivatives (n=3), lithium (n=1), orphenadrine (n=1), propiomazine (n=1), zopiclon (n=1) and zopiderm (n=1).

The control subjects were all Caucasians except one woman who was Asian, and none had any diagnosis of psychotic disorder (*Table 1*); neither did they use any drugs with anti-inflammatory effect that could influence their neurological disease, such as cortisone, interferon or cytostatics.

Laboratory analyses & clinical evaluation

The lumbar punctures and collections of blood samples were carried out in the morning after patients and control subjects had been fasting overnight, and then the samples were sent directly to the laboratory for analysis. Cerebrospinal fluid from patients and control subjects was analysed for albumin, IgG, cell counts and oligoclonal IgG; and S/P from patients and control subjects was analysed for albumin and IgG. In addition, S/P from patients was analysed for the inflammatory markers α1-antitrypsin, fibrinogen, haptoglobin, orosomukoid, IgA and IgM. All analyses were conducted with standard laboratory methods according to accredited routines by the Laboratory of Clinical Chemistry at the Karolinska University Hospital Solna, Stockholm, Sweden. The ratios of CSF-albumin to P-albumin and of CSF-IgG to S-IgG were calculated, as well as the IgG index according to the formula: (CSF-IgG: S-IgG ratio) divided by (CSF-albumin: P-albumin ratio) (Tibbling *et al.* 1977). The clinical evaluation of the patients was done on the day before the blood sampling by using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia (Kay *et al.* 1987; Von Knorring & Lindström 1992). The PANSS consists of four subscales of symptom complexes (positive symptoms, negative symptoms, positive and negative symptoms combined, and general psychiatric symptoms), each of the items is rated on different point scales.

Statistical methods

As the variables were assumed to be normally distributed, parametric methods were used in the statistical analyses. Continuous data were presented as mean and standard deviation (SD) or 95% confidence interval (CI), and categorical data were summarized using frequency counts and percentages. To compare groups of patients and control subjects regarding continuous variables the Student t-test was employed, and when controlling for sex and age a two-way analysis of covariance (ANCOVA) was conducted. In case of inhomogeneity of slopes, groups were compared at mean age. To compare groups of patients and control subjects regarding categorical variables, the chi-square or Fisher's exact tests were used. In subgroup analyses of patients, the same statistical tests were employed, apart from when controlling for heredity where a two-way main effects analysis of variance (ANOVA) was conducted. Moreover, Pearson's correlation coefficient (r) was calculated to measure the association between pairs of variables. A *p*-value of less than 0.05 was considered statistically significant. All calculations were done with the statistical program Statistica for Windows 13.0 (Dell Inc., Tulsa, OK, USA).

RESULTS

The mean (SD) of CSF and S/P levels and ratios in the patients and control subjects are given in *Table 2*. The CSF-albumin: P-albumin ratio was higher and the IgG index was lower in the patients than in the control subjects ($p = 0.045$ and $p = 0.001$, respectively; *Table 2; Figure 1a-b*). All patients and control subjects had IgG indices within the normal reference range, whereas five (33.3%) of the patients and two (16.7%) of the control subjects had slightly elevated CSF-albumin: P-albumin

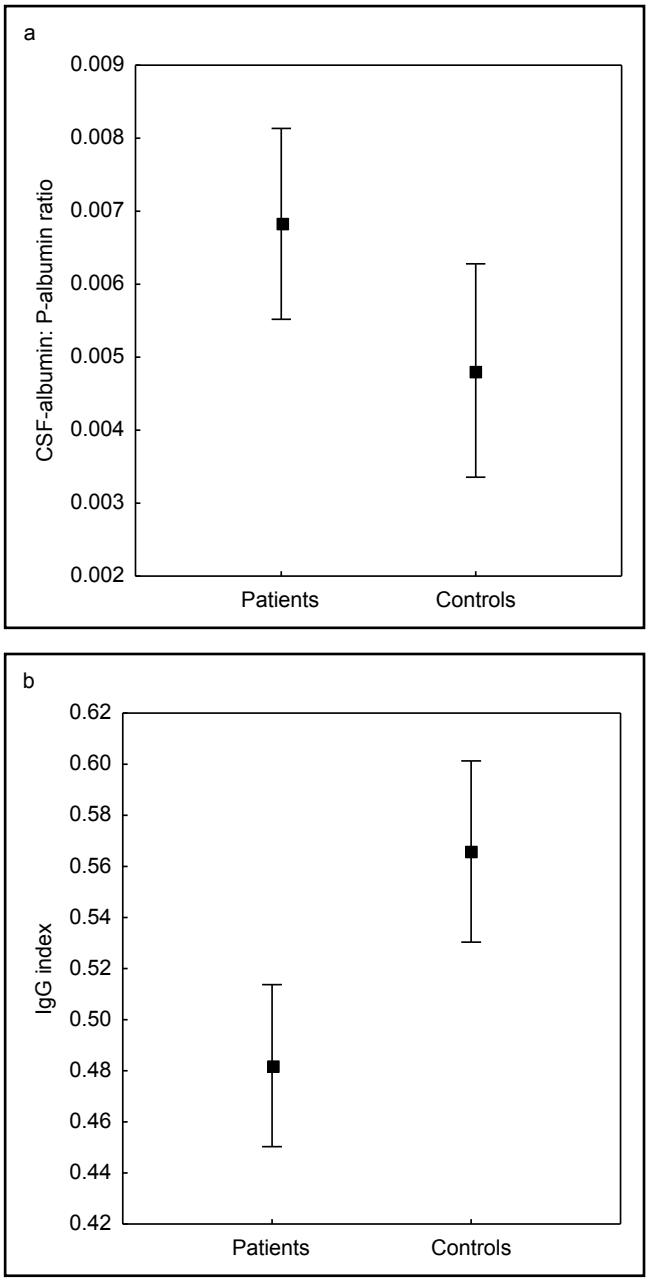

Fig. 1 a-b. The ratio of CSF-albumin to P-albumin (a) was higher and the IgG index (b) was lower in the patients than in the control subjects ($p = 0.045$ and $p = 0.001$, respectively). Solid square denotes the mean, and vertical bar the 95% confidence interval.

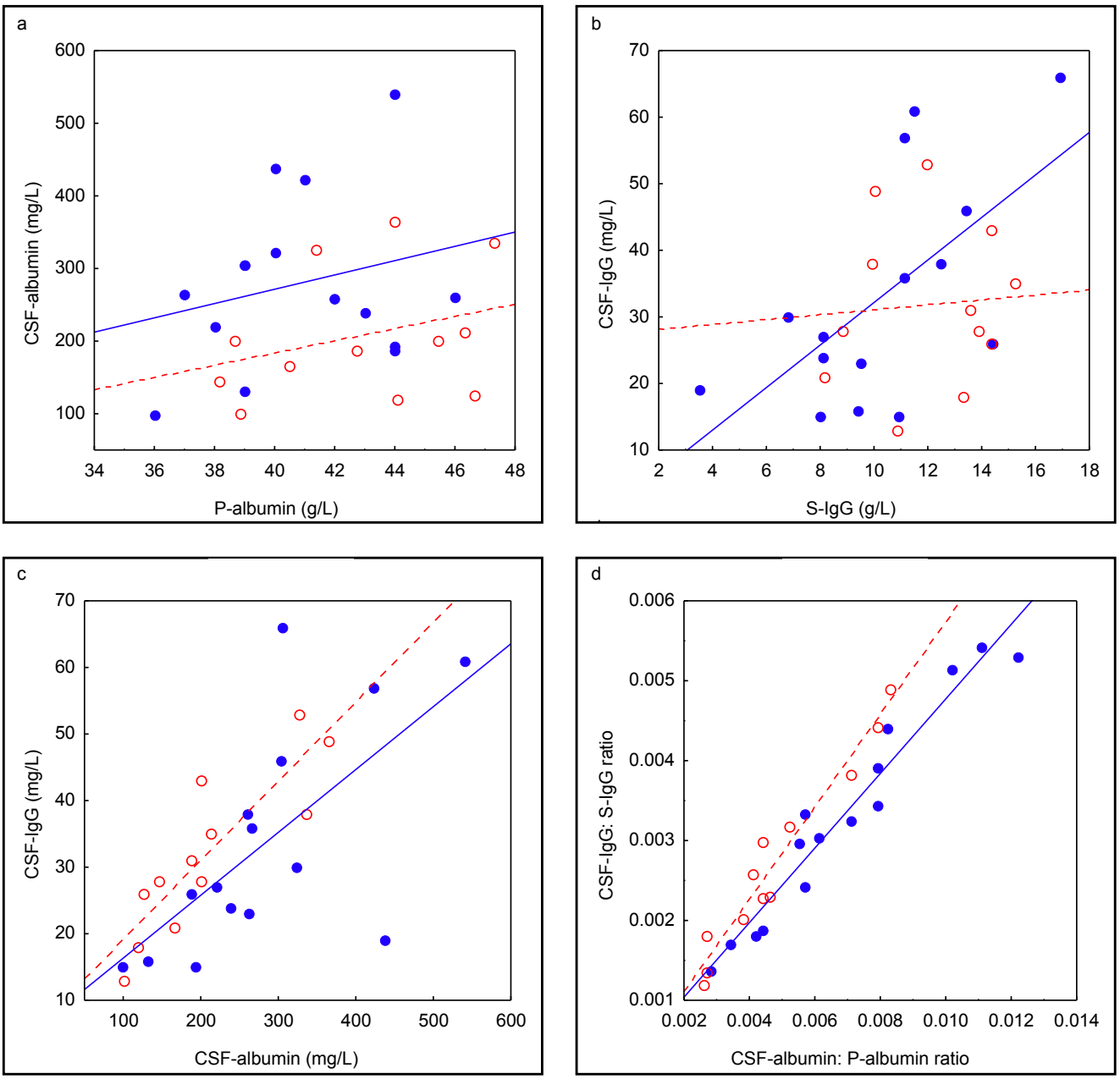

Fig. 2 a-d. Relationships between CSF-albumin and P-albumin (a), CSF-IgG and S-IgG (b), CSF-IgG and CSF-albumin (c), and CSF-IgG: S-IgG ratio and CSF-albumin: P-albumin ratio (d) in the patients and control subjects. Blue solid circles represent the patients (n = 15) and red open circles represent the control subjects (n = 12). Correlation coefficients for the relationships: **a)** No significant relationships; r = 0.25, $p = 0.378$ (patient group, solid blue line) and r = 0.31, $p = 0.325$ (control subject group, dotted red line). **b)** Significant relationship; r = 0.62, $p = 0.014$ (patient group, solid blue line), whereas no significant relationship; r = 0.07, $p = 0.822$ (control subject group, dotted red line). **c)** Significant relationships; r = 0.65, $p = 0.008$ (patient group, solid blue line) and r = 0.87, $p < 0.001$ (control subject group, dotted red line). **d)** Significant relationships; r = 0.97, $p < 0.001$ (patient group, solid blue line) and r = 0.97, $p < 0.001$ (control subject group, dotted red line)

ratios above the upper limit of normal reference range, and four (26.7%) of the patients and two (16.7%) of the control subjects had slightly elevated CSF-IgG levels above the upper limit of normal reference range (*Table 2; Figure 2a-b*). Further, one patient and one control subject had slightly elevated counts of polynuclear leukocytes in CSF (1×10^6/L), otherwise all had CSF-cell counts within the normal reference ranges (mononuclear leukocytes: $0–5 \times 10^6$/L; polynuclear leukocytes: $< 1 \times 10^6$/L), and none showed any signs of oligoclonal IgG-bands at CSF-elphoresis.

The S/P levels of albumin and IgG did not differ between patients and control subjects and were all in the main within the normal reference ranges (35–48 g/L and 7.0–15.0 g/L, respectively; data not shown). In addition, S/P levels of α1-antitrypsin, fibrinogen,

Tab. 1. Characteristics of the patients and control subjects studied

	Ethnicity, n	Age[a], y	Smoking, n (%)	Diagnosis, n	Heredity for schizophrenia or related psychosis, siblings included[b], n (%)	Duration of psychotic disorder[a], y	Type of current antipsychotic, n	Treatment time with current antipsychotic[a], y
Patients All (n = 15)	Caucasian (n = 15)	42 (9)	5 (33.3)	Schizophrenia[c] (n = 14) Schizoaffective disorder[e] (n = 1)	10 (66.7)	17.2 (8.9)	Haloperidol (n = 1) Clozapine (n = 3) Olanzapine (n = 6) Risperidone (n = 5)	5.4 (4.1)
Men (n = 7)	Caucasian (n = 7)	40 (9)	0 (0.0)[d]	Schizophrenia[c] (n = 7)	3 (42.9)	16.9 (8.8)	Haloperidol (n = 1) Clozapine (n = 1) Olanzapine (n = 3) Risperidone (n = 2)	5.9 (5.8)
Women (n = 8)	Caucasian (n = 8)	44 (9)	5 (62.5)	Schizophrenia[c] (n = 7) Schizoaffective disorder[c] (n = 1)	7 (87.5)	17.5 (9.7)	Haloperidol (n = 0) Clozapine (n = 2) Olanzapine (n = 3) Risperidone (n = 3)	5.0 (2.2)
Control subjects All (n = 12)	Caucasian (n = 11) Asian (n = 1)	43 (9)	nda	Non-inflammatory neurological disease (n = 12)	nda	na	na	na
Men (n = 4)	Caucasian (n = 4)	42 (10)	nda	Non-inflammatory neurological disease (n = 4)	nda	na	na	na
Women (n = 8)	Caucasian (n = 7) Asian (n = 1)	44 (9)	nda	Non-inflammatory neurological disease (n = 8)	nda	na	na	na

Abbreviations: n = number, na = not applicable, nda = no data available, y = year
[a] The data are given as mean (SD)
[b] I.e. patients who had one or more first-, second-, third-, or fourth-degree relatives, siblings included, with schizophrenia or related psychosis (Melkersson 2009)
[c] According to DSM-5 (American Psychiatric Association 2013)
[d] Significantly different compared to the women, $p = 0.026$

Tab. 2. CSF-albumin, CSF-IgG, CSF-albumin: P-albumin ratio, CSF-IgG: S-IgG ratio and IgG index in the patients with schizophrenia or related psychosis, compared to that of the control subjects

Laboratory parameter	CSF-albumin (mg/L)	CSF-IgG (mg/L)	CSF-albumin: P-albumin ratio	CSF-IgG: S-IgG ratio[a,b]	IgG index
Normal reference range	17 - 30 y: 80 - 260 31 - 40 y: 80 - 280 41 - 50 y: 80 - 320 > 50 y: 80 - 400	< 45	< 50 y: < 7 x 10^{-3} > 50 y: < 9 x 10^{-3}	17 - 30 y: 1.7 x 10^{-3} (0.5 x 10^{-3}) 31 - 40 y: 1.9 x 10^{-3} (0.5 x 10^{-3}) 41 - 50 y: 2.1 x 10^{-3} (0.7 x 10^{-3}) 51 - 60 y: 2.5 x 10^{-3} (0.7 x 10^{-3}) 61 - 77 y: 2.6 x 10^{-3} (0.9 x 10^{-3})	< 0.70
Patients (n = 15)[b]	279 (118)	33 (17)	6.8 x 10^{-3} (2.8 x 10^{-3})	3.3 x 10^{-3} (1.3 x 10^{-3})	0.48 (0.05)
	vs	vs	vs	vs	vs
Control subjects (n = 12)[b]	207 (89)	32 (12)	4.8 x 10^{-3} (2.0 x 10^{-3})	2.7 x 10^{-3} (1.2 x 10^{-3})	0.57 (0.07)
***P*-value[c]**	0.092 [0.121]	0.819 [0.920]	**0.045** [0.060]	0.270 [0.280]	**0.001 [0.047[d], 0.015[e]]**

Abbreviations: CSF = cerebrospinal fluid, n = number, P = plasma, S = serum, vs = versus, y = years
[a] Normal reference range according to Tibbling *et al.* (1977)
[b] The data are given as mean (SD)
[c] A significant difference is written in bold text, and *p*-values adjusted for sex and age are given in square brackets
[d] Male patients at mean age 42 y vs male control subjects at mean age 42 y
[e] Female patients at mean age 42 y vs female control subjects at mean age 42 y

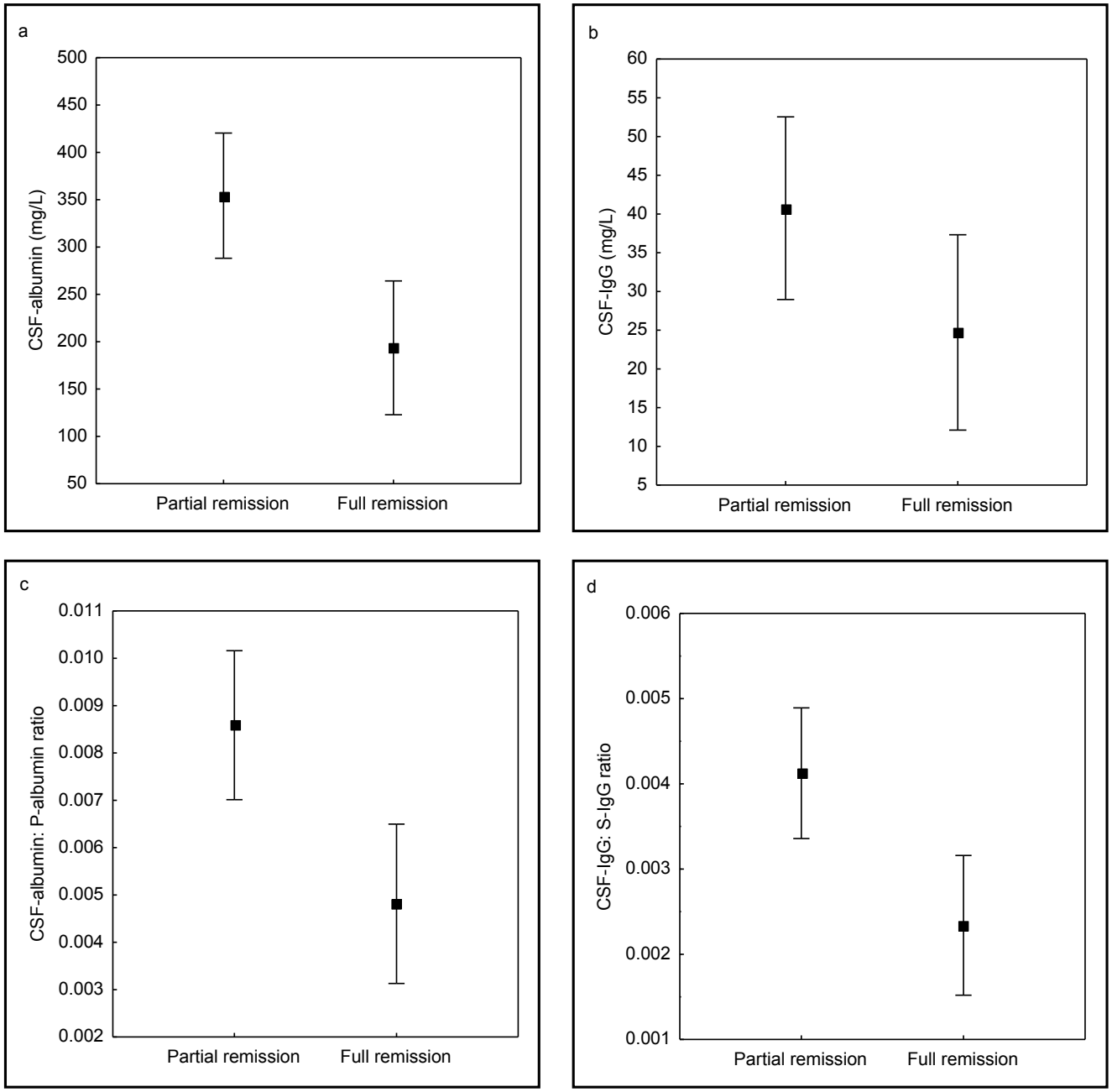

Fig. 3 a-d. CSF-albumin (a), CSF-IgG (b), CSF-albumin: P-albumin ratio (c) and CSF-IgG: S-IgG ratio (d) were higher, or displayed a tendency towards higher values, in the patients in partial remission (n = 8) than in the patients in full remission (n = 7) ($p = 0.003$, $p = 0.066$, $p = 0.004$ and $p = 0.004$, respectively). Solid square denotes the mean, and vertical bar the 95% confidence interval.

haptoglobin, orosomukoid, IgA and IgM were mainly within the normal reference ranges in all patients (data not shown).

The CSF-albumin level did not correlate to the P-albumin level in the patients or control subjects (*Figure 2a*), whereas the CSF-IgG level correlated positively to the S-IgG level in the patients, but not in the control subjects (*Figure 2b*). Further, positive correlations were found for both the patients and control subjects between the levels of CSF-IgG and CSF-albumin (*Figure 2c*), and between the ratios of CSF-IgG to S-IgG and of CSF-albumin to P-albumin (*Figure 2d*).

CSF-albumin, CSF-IgG, CSF-albumin: P-albumin ratio, CSF-IgG: S-IgG ratio or IgG index did not correlate to age, duration of psychotic disorder or treatment time with current antipsychotic in the 15 patients investigated. Neither were any significant associations found in the patients with smoking or type of current antipsychotic used and these parameters.

Remission states and mean PANSS scores in the 15 patients are shown in *Table 3*. Eight (53%) of the patients were in partial remission regarding clinical symptoms and 7 (47%) were in full remission

Tab. 3. Remission states and PANSS scores in the patients, as well as their relations to CSF-albumin, CSF-IgG, CSF-albumin: P-albumin ratio, CSF-IgG: S-IgG ratio and IgG index

Remission state	n (%)	Differences between subgroups[a,b]				
		CSF-albumin (mg/L)	CSF-IgG (mg/L)	CSF-albumin: P-albumin ratio	CSF-IgG: S-IgG ratio	IgG index
Partial	8 (53)	354 (103)	41 (19)	8.6×10^{-3} (2.4×10^{-3})	4.1×10^{-3} (1.1×10^{-3})	0.48 (0.05)
		vs	vs	vs	vs	vs
Full	7 (47)	194 (62)	25 (10)	4.8×10^{-3} (1.5×10^{-3})	2.3×10^{-3} (0.8×10^{-3})	0.48 (0.06)
P-value[c]		**0.003 [0.005]**	**0.066 [0.080]**	**0.004 [0.006]**	**0.004 [0.006]**	0.969 [0.822]
PANSS	**Scores[a]**	**Correlations[b]**				
		CSF-albumin	CSF-IgG	CSF-albumin: P-albumin ratio	CSF-IgG: S-IgG ratio	IgG index
Positive symptoms (reference range 7 - 49)	11 (3)	r = 0.45 *p* = **0.093**	r = 0.29 *p* = 0.302	r = 0.46 *p* = **0.085**	r = 0.45 *p* = **0.090**	r = 0.07 *p* = 0.794
Negative symptoms (reference range 7 - 49)	9 (1)	r = 0.05 *p* = 0.848	r = 0.09 *p* = 0.763	r = 0.03 *p* = 0.919	r = 0.02 *p* = 0.938	r = -0.11 *p* = 0.703
Positive and negative symptoms combined[d] (reference range -42 - +42)	1 (4)	r = 0.38 *p* = 0.162	r = 0.23 *p* = 0.411	r = 0.40 *p* = 0.144	r = 0.39 *p* = 0.148	r = 0.09 *p* = 0.742
General psychiatric symptoms (reference range 16 - 112)	21 (3)	r = 0.45 *p* = **0.090**	r = 0.43 *p* = 0.111	r = 0.47 *p* = **0.074**	r = 0.51 *p* = **0.051**	r = 0.34 *p* = 0.220

Abbreviations: CSF = cerebrospinal fluid, n = number, P = plasma, PANSS = Positive and Negative Syndrome Scale, r = Pearson's correlation coefficient, S = serum, vs = versus

[a]The data are given as mean (SD)

[b]A significant or a tendency towards a significant difference/ correlation is written in bold text

[c]*P*-values adjusted for heredity for schizophrenia or related psychosis (siblings included) are given in square brackets

[d]I.e. positive symptom scores minus negative symptom scores

(*Table 3*). No sex differences were found, either in remission states or PANSS scores.

CSF-albumin, CSF-IgG, CSF-albumin: P-albumin ratio and CSF-IgG: S-IgG ratio, but not IgG index, were higher, or displayed a tendency towards higher values, in the patients in partial remission than in the patients in full remission (*Table 3; Figure 3 a-d*). Moreover, the PANSS scores of positive symptoms or general psychiatric symptoms in the patients correlated, or tended to correlate, with CSF-albumin, CSF-albumin: P-albumin ratio or CSF-IgG: S-IgG ratio, but not with CSF-IgG or IgG index (*Table 3*).

The IgG index was lower in the patients with heredity for schizophrenia or related psychosis (siblings included) (n = 10) than in the patients without heredity (n = 5) [0.46 (0.04) versus 0.53 (0.05), $p = 0.009$; *Figure 4*], whereas no differences were found between the patients with or without heredity in CSF-albumin, CSF-IgG, CSF-albumin: P-albumin ratio or CSF-IgG: S-IgG ratio.

A graphical presentation of the results for the summarized evaluation of BBB function by the CSF-albumin: P-albumin ratio and of IgG synthesis within the CNS by the IgG index is shown in *Figure 5*. The patients had more often signs of both impaired BBB function and lower CNS IgG synthesis, compared to the control subjects (*Figure 5*). It was in particular the patients in partial remission, compared to those in full remission, that more often had signs of impaired BBB function; and the patients with heredity for schizophrenia or related psychosis, compared to those without heredity, that more often had signs of lower CNS IgG synthesis (*Figure 5*).

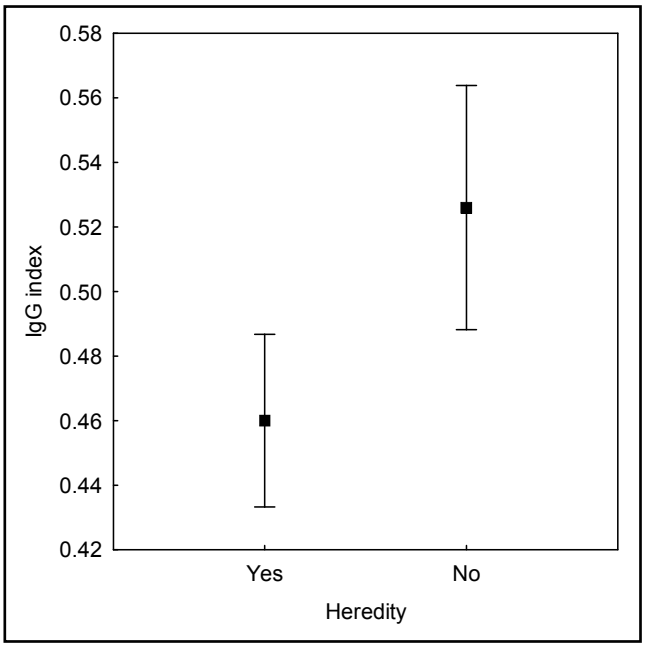

Fig. 4. The IgG index was lower in the patients with heredity for schizophrenia or related psychosis (siblings included) (n = 10) than in the patients without heredity (n = 5) ($p = 0.009$). Solid square denotes the mean, and vertical bar the 95% confidence interval.

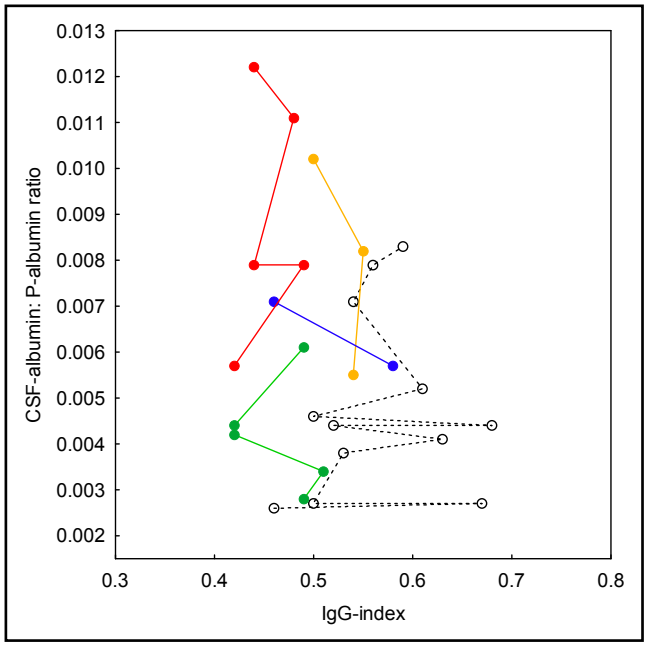

Fig. 5. Graphical presentation of the results for the summarized evaluation of BBB function by the CSF-albumin: P-albumin ratio and of IgG synthesis within the CNS by the IgG index, in the patients and control subjects. Red figure (**...•...**) indicates patients in partial remission with heredity for schizophrenia or related psychosis (n = 5), green figure (**...•...**) patients in full remission with heredity for schizophrenia or related psychosis (n = 5), yellow figure (**...•...**) patients in partial remission without heredity for schizophrenia or related psychosis (n = 3), blue figure (**...•...**) patients in full remission without heredity for schizophrenia or related psychosis (n = 2), and black figure (**---o---**) indicates control subjects (n = 12).

DISCUSSION

In this study we show that patients with a diagnosis of schizophrenia or schizoaffective disorder and on-going clinical symptoms have higher ratio of CSF-albumin to P-albumin, than patients with schizophrenia or schizoaffective disorder in full symptom remission or control subjects, indicating that the on-going psychotic disease process is connected with impaired BBB function. We also show that patients with a diagnosis of schizophrenia or schizoaffective disorder and heredity for schizophrenia or related psychosis have lower IgG index, than patients without heredity or control subjects, pointing to a reduced IgG synthesis within the CNS in particular in these patients. Further, CSF-IgG correlated positively to S-IgG only in the patients with a diagnosis of schizophrenia or schizoaffective disorder, and not in the control subjects, which would seem to be linked principally to the four patients with elevated CSF-IgG levels.

These present findings are supported by earlier published studies showing that an inflammatory, possibly autoimmune-mediated, process within the CNS (Al-Diwani *et al.* 2017; Benros *et al.* 2011; Bergink *et al.* 2014; Ermakov *et al.* 2017; Laskaris *et al.* 2016; Trépanier *et al.* 2016; Wetterberg *et al.* 2002), in combination with an aberrant immune system (Braun *et al.* 2017; Horváth & Mirnics 2014; Miller *et al.* 2011; Müller *et al.* 2000; Upthegrove *et al.* 2014), may underlie the development of schizophrenia, at least in a subgroup of patients.

Previously, several more CSF-alterations have been reported in patients with schizophrenia, such as decreased levels of brain-derived neurotrophic factor, nerve growth factor, peptide YY, homovanillic acid and calcium, decreased ratio of glutamate to glutamine, and increased levels of sICAM-1 and sCD14 (Hashimoto *et al.* 2005; Jimerson *et al.* 1979; Johansson *et al.* 2017; Kale *et al.* 2009; Melkersson 2010; Melkersson *et al.* 2015; Pillai *et al.* 2010; Raedler & Wiedemann 2006; Schwarz *et al.* 1998; Vasic *et al.* 2012; Widerlöv *et al.* 1988), together giving further support for an on-going pathological process within the CNS in schizophrenia.

To compare, our finding in this study that 33% of the patients with schizophrenia or related psychosis had slightly elevated ratios of CSF-albumin to P-albumin is fully in line with previous studies, reporting slightly increased CSF-albumin: P-albumin ratios in 22–29% of patients with schizophrenia (Bechter *et al.* 2010; Kirch *et al.* 1985, 1992; Müller & Ackenheil 1995). Concerning previous studies of IgG index in patients with schizophrenia, Kirch et al. (1985, 1992) found that 20–33% of patients had increased IgG indices. However, this was explained by the fact that their patients with increased IgG indices were more likely to have undergone electroconvulsive therapy (ECT) than their patients with normal IgG indices (Kirch *et al.* 1985, 1992). In this study, none of the patients had undergone ECT. They exhibited IgG indices within the normal reference, but lower indices than the control subjects, and lower than if they had heredity for schizophrenia or related psychosis.

Tendencies to correlations between PANSS scores of positive symptoms, but not of negative symptoms, and CSF-albumin, CSF-albumin: P-albumin ratio or CSF-IgG: S-IgG ratio were found in this study. These findings stand in contrast to those in the study by Müller & Ackenheil (1995), showing significant correlations between Scale for Assessment of Negative Symptom (SANS) scores and CSF-albumin or CSF-IgG in patients with schizophrenia. This discrepancy in findings can however be explained in that different scales for assessment of symptoms were used in our and their study, and also in that patients in the two studies differed according to degree of on-going psychotic symptomatology (Müller & Ackenheil 1995).

Limitations of this study include its smaller sample size, which may limit the generalizability of the findings and require replication in studies with larger numbers of patients and control subjects. Strengths of the study, on the other hand, include the comprising of a group of control subjects with neither inflammatory neurological diseases nor psychotic disorders.

In conclusion, we show that subgroups of patients with schizophrenia or related psychosis have a combination of impaired BBB function and lower IgG synthesis within the CNS. These findings are of importance since they contribute to increased understanding of the pathophysiology of schizophrenia and underline the relevance of further search for schizophrenia-antigens.

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