Upregulation of sICAM-1 and sVCAM-1 Levels in the Cerebrospinal Fluid of Patients with Schizophrenia Spectrum Disorders

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Research Article

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Abstract

Introduction

Immunological explanatory approaches are becoming increasingly important in schizophrenia research. In this context, the function of the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier (BCSFB) play an essential role. Different adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are key elements in sustaining the integrity of the BBB and BCSFB. The objectives of this study were (1) to compare the levels of different cell adhesion molecules in the CSF of patients with schizophrenia spectrum disorders to those of patients with unipolar depression and (2) to analyze their association with the established markers of the BBB/BCSFB function (total protein and albumin quotient [AQ]).

Patients and methods

A total of 40 patients with schizophrenia spectrum disorder and 39 age- and sex-matched control patients with unipolar depression were analyzed. The levels of soluble ICAM-1 (s-ICAM-1), soluble VCAM-1 (s-VCAM-1), and plasminogen activator inhibitor 1 (PAI-1) in the CSF were measured using a magnetic bead multiplexing immunoassay.

Results

The levels of sICAM-1 ($p<0.001$), sVCAM-1 ($p<0.001$), and PAI-1 ($p<0.001$) in the CSF were significantly higher in patients with schizophrenia spectrum disorder than in patients with unipolar depression. Correlation analyses revealed a significant correlation of protein concentrations with sVCAM-1 levels ($r=0.505$, $p=0.001$) and of AQs with the sVCAM-1 ($r=0.583$, $p<0.001$) and PAI-1 ($r=0.337$, $p=0.033$) levels in patients with schizophrenia.

Limitation

The significance of the study is limited by the retrospective research design and by the absence of a healthy control group. The assay used was not previously established for the measurement of CSF.

Discussion

Results revealed that sICAM-1 and sVCAM-1 levels in the CSF are higher in patients with schizophrenia spectrum disorder than in patients with depression. These circulating signaling molecules may indicate endothelial dysfunction causing impaired BBB/BCSFB function in patients with schizophrenia spectrum disorders. Consistent with this view, a highly significant correlation of sVCAM-1 with CSF protein and AQs was detected. Upregulation of these cell adhesion molecules might be indicative of a proinflammatory immune response underlying the BBB/BCSFB disturbance in a subgroup of patients with schizophrenia spectrum disorders. Further translational and controlled studies on the role of different cell adhesion molecules in schizophrenia are needed.

1. Introduction

Immunological explanatory approaches are becoming increasingly important in schizophrenia research (Pollak et al., 2020). Schizophrenia spectrum disorders were interpreted by several authors as complex neuropsychiatric disorders involving an activated inflammatory response leading to mild neuroinflammation (Bechter, 2013; Muller, 2019; Müller et al., 2013; Nguyen et al., 2018; Stefanovic et al., 2016). In this context, the functions of the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier (BCSFB) play a central role (Pollak et al., 2018), and a number of clinical studies showed alterations in biomarkers associated with the BBB/BCSFB (Endres et al., 2020; Endres et al., 2015; Najjar et al., 2017; Najjar et al., 2013; Orlovska-Waast et al., 2019). The central nervous system (CNS) is surrounded by the dynamic and metabolically active CSF and is separated from the peripheral circulation by several barriers, the most prominent are the BBB and the BCSFB (Banks et al., 2010; Deisenhammer et al., 2006; Tumani et al., 2017; Wildemann et al., 2010). The BBB/BCSFB form the primary interface that exerts key functions in brain homeostasis and immune protection (Banks et al., 2010; Najjar et al., 2017). One of the most notable components responsible for barrier integrity are the brain capillary endothelial cells that sustain a paracellular pathway with a highly selective permeability mediated by selective transport vesicles and tight junctions (Carvey et al., 2009; Pollak et al., 2018; Serlin et al., 2015). In this cerebral microvascular endothelium, different intercellular adhesion molecules, particularly intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are expressed under chronic inflammatory conditions (Kong et al., 2018; Müller, 2019). Endothelial cells are not only a passive barrier but also immunologically active themselves. For example, they can produce chemokines (Blank et al., 2016), and endothelial VCAM-1 is associated with age- and inflammation-induced microglia activation, impaired neurogenesis and cognitive deficits. These changes are diminished by antagonization of VCAM-1 and can occur even without disturbance of the BBB/BCSFB parameters or infiltration of immune cells (Yousef et al., 2019).

Previous studies comparing patients with schizophrenia spectrum disorder and controls revealed contradictory findings on soluble ICAM-1 (sICAM-1) and soluble VCAM-1 (sVCAM-1) levels when obtained with different methods and samples, including serum, CSF, and postmortem CNS tissues, as summarized in Table 1 (Müller, 2019).

The objective of this study was to conduct the first controlled CSF study that investigates cell adhesion molecules in patients with schizophrenia spectrum disorders and in a psychiatric control group. More specifically, we (1) compared the levels of different cell adhesion molecules in the CSF of patients with schizophrenia spectrum disorders to those of patients with unipolar depression and (2) we analyzed the association of these cell adhesion molecules with the established CSF markers of BBB/BCSFB function (i.e., total CSF protein and albumin quotient [AQ]).

2. Participants And Methods

This study was part of a larger retrospective project that was approved by the local ethics committee (Faculty of Medicine, University of Freiburg, ethical vote no. 396/18). Lumbar punctures were performed after careful gathering of information and after obtaining written informed consent as part of clinical routine to rule out organic causes of psychiatric symptoms This study was carried out in accordance with relevant guidelines and regulations.

2.1 Study sample

A total of 40 patients diagnosed with schizophrenia spectrum disorder and 39 patients diagnosed with unipolar depression were included in this study (for clinical and demographic details see tables 2 and 3). Based on the predominant clinical syndrome, patients were classified according to the criteria set by the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). In the schizophrenia cohort, 13 patients went through their first episode and 27 suffered from a chronic or recurrent manifestation, with chronic being defined as a period of more than two years. In the depression cohort, 12 patients suffered from their first episode and 27 patients were in a chronic or recurrent stage. All 39 patients in the depression cohort were diagnosed with a severe depressive episode.

2.2 Cerebrospinal fluid analysis and instrumental diagnostics

The routine CSF analysis included the determination of white blood cell (WBC) count, protein concentration, AQ, immunoglobulin (Ig)G index, and oligoclonal bands (OCBs) according to an established methodology (c.f. Endres et al., 2015, 2020). The measurements were carried out in the CSF laboratory of the University Hospital Freiburg (https://www.uniklinik-freiburg.de/neurologie/klinik/diagnostische-einrichtungen/liquor-labor.html). Electroencephalography (EEG) and cerebral magnetic resonance imaging (MRI) were offered to all patients as part of the clinical routine work-up.

3. Measurement of cell-adhesions markers

The adhesion molecules were quantified through a magnetic bead-based multiplex immunoassay by using a Human Adhesion Magnetic 6-Plex Panel (ThermoFisher, Waltham, MA); a MAGPIX® machine (ThermoFisher, Waltham, MA) was used to read and analyze the assay. The panel utilized to investigate sICAM-1, sVCAM-1, plasminogen activator inhibitor 1 (PAI-1), P-selectin, E-selectin, and platelet endothelial cell adhesion molecule-1 (PECAM) was used in accordance with the manufacturer's specifications, with the exception of using undiluted CSF samples, as this panel was originally not established for CSF analysis. The reported values are corrected for the different dilution. To determine whether the calculated concentrations of the individual adhesion molecules were reliable, we investigated the mean fluorescent intensity after deduction of the blank value, which is known as the net median fluorescence intensity (NetMFI), as well as the number of magnetic beads measured per analyte per well (bead count; cf. Kuzior et al., 2020). In this study, all values with a NetMFI below the lowest standard of the standard curve of the respective cell adhesion molecule and all wells with a bead count below 20 were excluded (c.f. with Kuzior et al., 2020). Only the samples that were measurable (and therefore not

below the detection level) for >50% of the analytes were analyzed. The adhesion molecule concentrations below the detection level were set to zero.

2.4 Data handling and statistical analyses

Data was analyzed using the Statistical Package for the Social Sciences (SPSS), version 24 (IBM Corp., Armonk, NY). Group comparisons for categorical variables were conducted using the Pearson's chi-squared test, whereas group comparisons for continuous variables were performed using two-sided independent sample t-tests. A Pearson correlation between CSF basic parameters (WBC count, protein concentration, AQ, and IgG index) and cell adhesion molecules (sICAM-1, sVCAM-1, and PAI-1) was separately performed for each group (schizophrenia and unipolar depression). A p-value of <0.05 was set to indicate statistical significance. No correction for multiple testing was performed given that an exploratory approach was implemented in this study.

3. Results

3.1 Sociodemographic data

The sociodemographic data is summarized in Tables 2 and 3. The schizophrenia spectrum and depressive patient groups were matched for age (F=11.455, p=0.660) and sex (Chi^2=0.141, p=0.707).

3.2 Cell adhesion molecules in the cerebrospinal fluid

The cell adhesion molecules sICAM-1, sVCAM-1, and PAI-1 in the CSF were successfully measured. The other parameters could not be measured sufficiently. The levels of sICAM-1 (p<0.001), sVCAM-1 (p<0.001), and PAI-1 (p<0.001) in the CSF were significantly higher in the patients with schizophrenia spectrum disorder than in those with unipolar depression (Table 4). Subgroup analyses between patients with schizoaffective (N=11) and the other patients from the schizophrenia spectrum disorder group (N=29) had similar mean ages (F=0.213, p=0.345). Both groups did not differ in the concentrations of sICAM (F=0.042, p=0.541), sVCAM (F=3.029, p=0.054), and PAI (F=0.057, p=0.239). The sICAM-1, sVCAM-1, and PAI-1 levels in patients with first-episode schizophrenia spectrum disorder or depression did not significantly differ from those in patients with a chronic/recurrent state of the diseases (data not shown in detail).

3. Basic cerebrospinal fluid findings and instrumental diagnostics

The routine findings for CSF diagnostics are presented in Table 5. Overall, no significant differences in WBC counts, protein concentration, AQs, IgG indices, and rate of OCBs were observed between the schizophrenia and depression groups. Also, the number of total abnormalities in MRI (in 63% of patients with schizophrenia-spectrum disorders and in 67% of patients with depression; Chi^2=0.278, p=0.598) in the two groups did not differ significantly, although EEG pathologies occurred more frequently in the schizophrenia group (in 25%; versus in 5% of the patients with depression; Chi^2=6.053, p=0.014).

3.4 Correlation analyses

In the schizophrenia spectrum disorder cohort, the CSF total protein concentration correlated significantly with the sVCAM-1 levels (r=0.505, p=0.001), and the AQ correlated with the sVCAM-1 (r=0.583, p<0.001; see Figure 1) and PAI-1 levels (r=0.337, p=0.033). By contrast, the levels of the cell adhesion molecules were not significantly correlated with clinical features, including suicide attempts and the number of earlier inpatient stays. In the unipolar depression cohort, no significant correlations of sICAM-1, sVCAM-1, and PAI-1 levels with WBC count, CSF total protein, AQ, and IgG index were detected. Also, the levels of the adhesion molecules were not significantly correlated with clinical features, including suicide attempts and the number of earlier inpatient stays.

4. Discussion

The results of this study revealed significantly elevated sICAM-1 and sVCAM-1 levels in patients suffering from schizophrenia spectrum disorders compared to patients with depressive disorders. Oriented to established CSF reference values (using ELISA-technique) of sICAM according to which CSF values < 300 pg/mL must be assumed in healthy controls, the values in depressed patients (Mean: 466.205 pg/ml) have been found to be already slightly increased and those in schizophreniform disorders were clearly elevated and on average four times above the established reference value (Mean: 1196 pg/ml) (for reference values see: https://07525720-0688-4380-840d-0a4af942fef7.filesusr.com/ugd/92c932_454e4d6908d94f64b3623b621179eade.pdf). An upregulation of these signaling molecules in the schizophrenia spectrum disorder cohort may firstly be indicative of neuroinflammatory processes followed by a proinflammatory immune response (Müller, 2019; Ramos et al., 2014). Second, the overexpression of the adhesion molecules may be related to an impairment of the BBB/BCSFB (Müller, 2019; Schwarz et al., 1998). Accordingly, the sVCAM-1 levels correlated with the AQ (which is considered the gold standard estimating the integrity of the BBB/BCSFB) in patients with schizophrenia spectrum disorders (Pollak et al., 2018; Reiber et al., 2001; Reiber et al., 2018; Tumani et al., 2017; Wildemann et al., 2010).

4.1 Integration of our findings into the context of the current research

Increased sICAM-1 levels have been observed in multiple inflammatory and cell-mediated autoimmune disorders (Radu et al., 2020). The current findings of increased CSF levels of this molecule are consistent with the reported significant elevation of plasma sICAM-1 levels in patients with schizophrenia spectrum disorder (Cai et al., 2020; Stefanovic et al., 2016). Stefanovic et al. (2016) discerned increased sICAM-1 levels in patients at a late stage of the disease, whereas no difference between healthy controls and patients with schizophrenia spectrum disorder was found in the early disease stages. By contrast, decreased peripheral levels of sICAM-1 and sVCAM-1 have been reported in another cohort of patients with schizophrenia spectrum disorders (Schwarz et al., 2000). In the explanatory approach, these contradictory findings may be explained in the light of a dysfunctional neuroendocrine immune communication and a reduced immune response during the acute onset of schizophrenia, whereas an

overexpression could be an indication of an immune activation during a prolonged course of the disease (Müller, 2019; Nguyen et al., 2018). Consistent with this view, 68% (27 out of 40) of the patients with schizophrenia in the present cohort suffered from a recurrent/chronic course of the disease. However, we were not able to detect significant differences that distinguish patients with the first episode from those with the recurrent/chronic stage. In the first, uncontrolled CSF study on cell adhesion molecules in schizophrenia, a significant correlation was found between sICAM-1 level and AQs (Schwarz et al., 1998); this finding could not be replicated in our data. However, a significant positive correlation between sVCAM-1 levels and AQs was discerned (see Figure 1).

4.2 Pathophysiological and clinical considerations

An increase in circulating proinflammatory cytokines was determined in the context of multiple psychiatric disorders (Cai et al., 2020; Lawson et al., 2009; Nguyen et al., 2018). Different inflammatory mediators (e.g., TNFα, IL-1β, and IFNγ) induce the expression levels of ICAM-1 and VCAM-1 (Kong et al., 2018; Najjar et al., 2017; Najjar et al., 2013; Nguyen et al., 2018). ICAM-1 (CD54) is a transmembrane glycoprotein of approximately 100 kDa in size; it belongs to the immunoglobulin supergene family and it consists of five tandem immunoglobulin-like domains (Krönig et al., 2005; Lawson et al., 2009; Muller, 2019; Ramos et al., 2014). In the CNS, ICAM-1 is expressed most notably in microglial cells, astrocytes, and endothelial cells in the white and grey matter (Müller, 2019; Ramos et al., 2014). The ligations of ICAM-1 to the lymphocyte function-associated molecule 1 on the surface of endothelial cells and to the macrophage-associated antigen-1 receptors on leucocytes contribute to the immune cell infiltration during an inflammatory response (Cai et al., 2020; Krönig et al., 2005; Lawson et al., 2009). ICAM-1 enables the trans-endothelial migration of leukocytes to the site of inflammation and plays an important role in immunological synapse formation (the interaction between antigen-presenting cells and T cells), in lymphocyte activation, and in numerous cellular immune responses (Cai et al., 2020; Lawson et al., 2009; Muller, 2019; Radu et al., 2020; Ramos et al., 2014). Arising from alternative splicing and/or proteolytic cleavage of membrane-bound ICAM-1 messenger RNA, a circulating soluble form of ICAM-1 (sICAM-1) consisting of the complete extracellular domain can be found in serum and CSF (Krönig et al., 2005; Lawson et al., 2009; Ramos et al., 2014). The sICAM-1 and its membrane-bound form exert similar functions (Müller, 2019). The elevated levels of sICAM-1 in CSF—as demonstrated in the current study—or in serum may therefore be indicative of the upregulated state of the membrane-bound ICAM-1 in the brain (Müller, 2019). VCAM-1 (CD106) is a 90-kDa glycoprotein predominantly expressed in endothelial cells (Kong et al., 2018). VCAM-1 regulates the pathway involved in leukocyte recruitment and transendothelial migration during inflammation via the interaction of its domain 1 (and/or 4) with α4β1 integrin (Kong et al., 2018). In most cell types, the expression of leucocyte adhesion molecules, such as ICAM-1 and VCAM-1, is low under non-inflammatory conditions, whereas a state of overexpression was described in many pathological states, especially during chronic inflammatory processes (Kong et al., 2018; Muller, 2019; Pollak et al., 2018; Ramos et al., 2014). Given that ICAM-1 is widely expressed in tissues, ICAM-1 levels may thus indicate the general level of inflammation (Radu et al., 2020); by contrast, VCAM-1 seems to indicate the conditions of the cerebral endothelium and the dendritic cells more precisely and thus could be used to assess endothelial dysfunction (Radu et al., 2020). Correlations were observed between the

elevated levels of ICAM-1 and the progression and severity of cancer, cardiovascular disease, and autoimmune disorders (Lawson et al., 2009; Muller, 2019) as well as between VCAM-1 and the progression of various immunological disorders, including rheumatoid arthritis, and cancer (Kong et al., 2018). In patients with schizophrenia spectrum disorders, the current study showed evidence of upregulated ICAM-1 and VCAM-1 levels, which may partially reflect the occurrence of leukocyte transendothelial recruitment and adhesion (Müller, 2019). The overexpression of ICAM-1 and VCAM-1 near the endothelial layer of the vessel wall impairs the vascular endothelial mitochondrial oxidative metabolism and directly destabilizes endothelial tight junctions (Kong et al., 2018; Najjar et al., 2017; Najjar et al., 2013; Nguyen et al., 2018). These processes increase the BBB/BCSFB permeability and allow the inappropriate migration of pro-inflammatory molecules into the brain parenchyma, enabling interactions between the innate and the peripheral adaptive immune systems in the brain (Bechmann et al., 2007; Carvey et al., 2009; Kong et al., 2018; Najjar et al., 2017). These theoretical considerations are supported by the correlation found between the sVCAM-1 levels and AQs in this study. In addition, it was earlier demonstrated that ICAM-1 and VCAM-1 can be elevated without an “open BBB/BCSFB”. In a review by Varatharaj and Galea (2017), disruptive and non-disruptive changes in the BBB were compared. The fact that there was no severe barrier disruption across the entire present cohort, but already high sICAM-1 and sVCAM-1 levels, could indicate that non-disruptive changes are underlying the pathological processes here. Therefore, the tight junctions would not be affected, but the endothelia would still let pass immune cells and/or secrete cytokines/chemokines. Thus, from a clinical perspective, sICAM-1 and sVCAM-1 could provide further information about the BBB/BCSFB function in addition to established CSF parameters such as AQ.

4.3 Limitations

A limitation of the present study is its lack of a healthy control group. Especially with regard to CSF measurements. It is difficult to ethically justify lumbar punctures in a large group of healthy volunteers. Previously, we used a control group of patients with pseudotumor cerebri (e.g., Stich et al., 2015; Kuzior et al., 2020). In the current study, this approach was considered initially; unfortunately, we were unable to recruit a matched control group with an adequate sample size. However, we were able to use a clinical control group of patients with depressive disorders and established reference values. Patients with schizophrenia were routinely offered a lumbar puncture. In patients with depression, lumbar punctures were performed only in selected cases. These patients were not screened routinely and there probably is a selection bias towards severely depressed patients. In addition, the multiplexing immunoassay used was originally not established for CSF measurements, and its use may possibly have led to methodical inaccuracies and difficulties. However, most other methodological approaches have so far only been established for blood. Because CSF analysis was performed as part of clinical routine diagnostic work-up, the processes involved in sample processing were not completely standardized. The samples first underwent routine testing before being frozen at −80 °C. In future studies, samples should be processed directly according to established and pre-defined standard operating procedures. The influence of other possible contributing factors, including psychotropic medication or multiple vascular risk factors (Mantere et al., 2019; Muller, 2019; Nguyen et al., 2018), remains unclear and needs to be considered. In

addition, we were not able to examine serum samples of the patients. This would have been helpful for the overall interpretation and comparison with the preliminary studies, which mostly only examined serum material. Finally, it is important to keep in mind that an overexpression of ICAM-1 is observed in a wide range of diseases and inflammation, even in depressive disorders; therefore, the present findings in patients with schizophrenia spectrum disorder probably do not reflect disease-specific processes (Müller, 2019). Due to the limitations mentioned above, the present results are to be considered preliminary and warrant replication in future studies.

5. Conclusions

The schizophrenia spectrum disorder pathophysiology may involve an altered immune response and a disturbed communication between the CNS and the immune system due to an impaired BBB/BCSFB. The present results indicate that the circulating immune signaling molecules sICAM-1 and sVCAM-1 might play a relevant role in this context. Further translational, prospective, and controlled studies in this novel psychoneuroimmunological field of research are needed.

6. Declarations

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Authors' contributions: SMe, BLF, HK, LTvE and DE created the study design. BLF, KD, DE and LTvE supervised the study. HK and BLF were responsible for laboratory measurements. BB performed CSF basic analyses. SMe and SMa performed the statistical analyses. SMe wrote the paper and performed the data search. DE critically revised the manuscript. HK, KR, PS, KN, DD, MAS, MM, KB, KD, and LTvE supported the interpretation and revised the manuscript further. All authors were critically involved in the theoretical discussion and composition of the manuscript. All authors read and approved the final version of the manuscript.

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Tables

Table 1: Overview of findings measuring levels of sICAM-1 and sVCAM-1 in patients with schizophrenia-spectrum disorders (reviewed by Müller, 2019). Abbreviations: CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; sICAM-1, soluble intercellular adhesion molecule 1; BCSFB, blood-CSF-barrier; PCR, polymerase chain reaction; mRNA, messenger RNA; VEGF, vascular endothelial growth factor; sVCAM-1, vascular cell adhesion molecule 1; ↑, higher; =, normal; ↓, lower; Ø, none.

Sample material	Method	Research group	Schizophrenia-spectrum disorder group	Control group	Results
CSF	ELISA	Schwarz et al., 1998	n=40	Ø	Significant association of sICAM-1 and BCSFB
CSF	ELISA	Schwarz et al., 2000	n=18	Ø	Significant positive correlation of sICAM-1 with negative symptomatology and disease duration
Cortex tissue	PCR	Cai et al., 2018	n=37	n=37	↑ expression of ICAM-1 mRNA
Plasma	Multiplexing immuneassay (Luminex®)	Cai et al., 2018	n=78	n=73	↑ levels of sICAM-1
Plasma	Multiplexing immuneassay (Meso Scale Discovery MULTI-SPOT®)	Nguyen et al., 2018	n=134	n=113	↑ levels of 'vascular endothelial index' including VEGF, sICAM-1, sVCAM-1
Serum	ELISA	Schwarz et al., 2000	n=72	n=38	↓ levels of sICAM-1 and increase of sICAM-1 during treatment
Serum	ELISA	Kroenig et al., 2005	n=70	n=128	↓ levels of sICAM-1 and relationship to ICAM-1 G214A polymorphism
Serum	ELISA	Stefanovic et al., 2016	n=80	n=80	= levels of sICAM-1 in early-stage, ↑ levels of sICAM-1 in late-stage and associations with severity and disease duration

Table 2: Clinical data of patients with schizophrenia-spectrum disorder and depressive disorder.

Abbreviations: CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, EEG = electroencephalography, F = female, M = male, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, SSNRI = selective serotonin/noradrenaline reuptake inhibitor.

	Schizophrenia-spectrum disorder (N=40)	Depressive disorder (N=39)
Sex	16 M : 24 F	14 M : 25 F
Age (Mean±SD, range)	33.63 ± 13.38	32.54 ± 7.65
	(18-65years)	(18-44 years)
Clinical syndrome and characteristics		
Severe depressive episode		39 (100%)
With psychotic symptoms		7 (18%)
Without psychotic symptoms	40 (100%)	32 (82%)
	25 (63%)	
Schizophrenia spectrum disorder	1 (3%)	
	1 (3%)	
Paranoid-hallucinatory	1 (3%)	
Hebephrenic	11 (28%)	
Catatonic	6 (15%)	
Delusional disorders	3 (8%)	
Schizoaffective	2 (5%)	
- Depressive	1 (3%)	
- Manic		
- Mixed		
Acute polymorphic psychotic		
Course of disease		
Recurrent/chronic	27 (68%)	27 (69%)
First episode	13 (33%)	12 (31%)
Neurologic comorbidity		
Seizures/Attacks	2 (5%)	0 (0%)
Traumatic	3 (8%)	0 (0%)
Polyneuropathy	0 (0%)	0 (0%)
Migraine/Headache	1 (3%)	1 (3%)
Overall	6 (15%)	1 (3%)
Psychotropic medication		

at the time of sampling		
SSRI	4 (10%)	9 (23%)
SSNRI	1 (3%)	21 (54%)
Tricyclic antidepressants	0 (0%)	8 (21%)
Bupropion	4 (10%)	4 (10%)
Mirtazapine	1 (3%)	6 (15%)
Typical neuroleptics	9 (23%)	4 (10%)
Atypical neuroleptics	40 (100%)	21 (54%)
Lithium	7 (18%)	9 (23%)
Anticonvulsant	7 (18%)	1 (3%)
Benzodiazepine	9 (23%)	3 (8%)
Unmedicated	0 (0%)	2 (5%)

Table 3: Demographic data.

	Schizophrenia-spectrum disorder (N=40)	Depressive disorder (N=39)
Marital status		
Single	30 (77%)	31 (79%)
Married	6 (15%)	6 (15%)
Divorced	1 (3%)	2 (5%)
Widowed	1 (3%)	0 (0%)
Unknown	2 (5%)	0 (0%)
Level of education		
Low	11 (28%)	2 (5%)
Middle	7 (18%)	8 (21%)
High	19 (48%)	28 (72%)
Unknown	3 (8%)	1 (3%)
Work situation		
Unemployed	7 (18%)	6 (15%)
Working	13 (33%)	20 (51%)
In training	11 (28%)	11 (28%)
Retired	6 (15%)	1 (3%)
Housewife/-man	2 (5%)	1 (3%)
Unknown	1 (3%)	0 (0%)
Housing situation		
Alone	13 (33%)	18 (47%)
With partner/family	11 (28%)	10 (26%)
With parents/guardian	12 (30%)	10 (26%)
Other	4 (10%)	0 (0%)
Unknown	0 (0%)	1 (3%)
Suicide attempts		
None		34 (87%)

One	28 (70%)	2	2 (5%)
Two	(5%)	4	2 (5%)
Three	(10%)	1	0 (0%)
Four	(3%)	1	0 (0%)
Five	(3%)	1	0 (0%)
Six	(0%)	0	1 (3%)
Unclear		3 (8%)	0 (0%)
Number of earlier inpatient treatments			
None	12 (30%)		15 (38%)
One	6 (15%)		12 (31%)
Two	3 (8%)		6 (15%)
Three	3 (8%)		2 (5%)
Four	2 (5%)		1 (3%)
Five	5 (13%)		2 (5%)
> Five	7 (18%)		1 (3%)
Unclear	2 (5%)		0 (0%)

Table 4: Cell adhesion molecule levels in the cerebrospinal fluid. Abbreviations: PAI-1 = plasminogen activator inhibitor 1, SD = standard deviation, s-ICAM-1 = soluble intercellular adhesion molecule-1, sVCAM-1 = soluble vascular cell adhesion molecule-1.

	Schizophrenia-spectrum disorder (N=40)	Depressive disorder (N=39)	Statistics
PAI-1 (pg/ml) (Mean ± SD)	72.006 ± 46.810	30.756 ± 23.397 (N=38)	**F= 13.312** **p<0.001**
sICAM-1 (pg/ml) (Mean ± SD)	1196.252 ± 768.714	466.205 ± 277.053	**F=12.716** **p<0.001**
sVCAM-1 (pg/ml) (Mean ± SD)	456.197 ± 155.549	234.195 ± 151.553	**F=0.239** **p<0.001**

Table 5: Findings in cerebrospinal fluid routine diagnostics. Abbreviations: WBC = white blood cell, SD = standard deviation, y. = years, IgG = immunoglobulin G, CSF = cerebrospinal fluid, OCBs = oligoclonal bands. * Two findings were borderline positive: A first patient had some weak identical bands in CSF and serum, a second patient had an isolated OCB in the CSF.

	Reference	Schizophrenia-spectrum disorder (N=40)	Depressive disorder (N=39)	Statistics
WBC counts (Mean ± SD)	in /µl	1.85 ± 1.46	1.82 ± 1.23	F=0.066 p=0.923
Number of increased WBC counts	< 5 /µl	↑: 3 (8%)	↑: 2 (5%)	Chi^2=0.187 p=0.665
Protein concentration (Mean ± SD)	in mg/l	406.45 ± 196.15	418.87 ± 153.68	F=0.599 p=0.755
Number of increased protein concentration	< 450 mg/l	↑: 12 (30%)	↑: 14 (36%)	Chi^2=0.311 p=0.577
Albumin quotient (Mean ± SD)		5.02 ± 2.29	5.12 ± 2.05	F=0.158 p=0.834
Number of increased albumin quotients	<40y.: < 6.5 x 10^{-3} 40-60y.: < 8 x 10^{-3} >60y.: < 9.3 x 10^{-3}	↑: 6 (15%)	↑: 8 (21%)	Chi^2=0.412 p=0.521
IgG-Index (Mean ± SD)	in mg/l	0.49 ± 0.04	0.49 ± 0.09	F=1.813 p=0.731
Number of increased IgG indices	< 0.7 mg/l	↑: 0 (0%)	↑: 1 (3%)	Chi^2=1.039 p=0.308
OCBs in CSF	negative	1* (3%)	2 (5%)	Chi^2=0.556 p=0.346

Figures

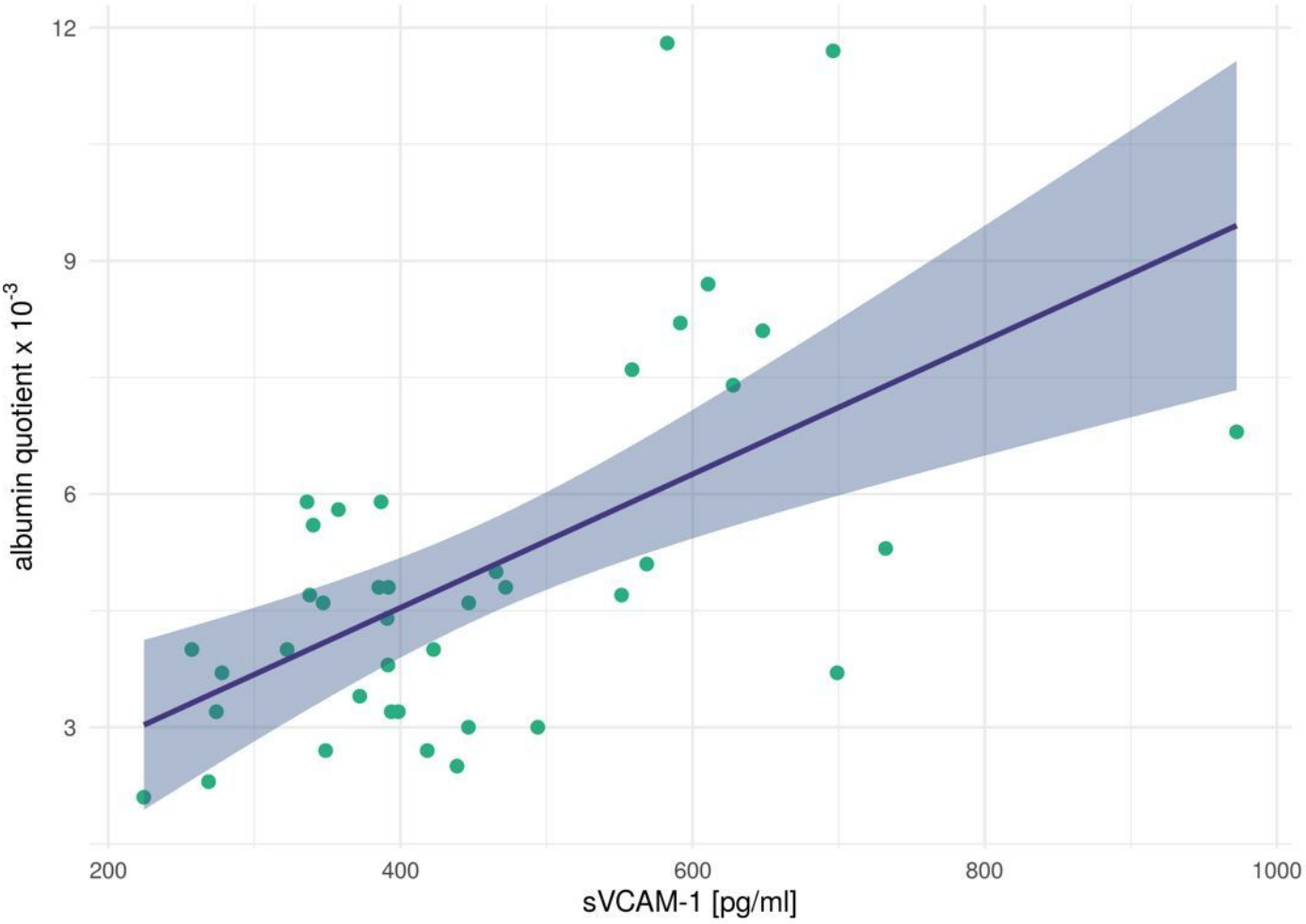

Figure 1

The albumin quotient significantly correlated with the vascular cell adhesion molecule-1 in patients with schizophrenia spectrum disorders (sVCAM-1; r=0.583, p<0.001).