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Cerebrospinal Fluid Pathologies in Schizophrenia-Spectrum Disorder—A Retrospective Chart Review

Mattia Campana*[,1,4], Johanna Strauß[1,4], Susanne Münz[1], Tatiana Oviedo-Salcedo[1], Piyumi Fernando[2], Peter Eichhorn[3], Peter Falkai[1], Alkomiet Hasan[2], and Elias Wagner[1]

[1]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany; [2]Department of Psychiatry, Psychotherapy and Psychosomatics, University of Augsburg, Augsburg, Germany; [3]Institute of Laboratory Medicine, University Hospital, LMU Munich, Munich, Germany; [4]These authors contributed equally to this work.

*To whom correspondence should be addressed; Department of Psychiatry and, Psychotherapy, LMU Munich, Nussbaumstraße 7, D-80336 Munich, Germany; tel.: 49-89-4400-55505, fax: 49-89-4400-55530, e-mail: Mattia.Campana@med.uni-muenchen.de

Background: **The role of inflammatory processes in the etiology of schizophrenia is increasingly being investigated. A link between psychosis and inflammation measured with different biomarkers has been reported in the literature and needs to be further explored. To investigate the presence of inflammatory biomarkers in first-episode psychosis (FEP) we analyzed the largest available FEP cohort to date regarding routine CSF and blood diagnostics.*Methods:* We report a retrospective analysis of clinical data from all inpatients that were admitted to our tertiary care hospital with a ICD-10 diagnosis of F2x (schizophrenia-spectrum) between January 1, 2008 and August 1, 2018 and underwent a lumbar puncture.*Results:* A total of n = 314 FEP patients were included in our sample. 42.7% patients (134/314) showed cerebrospinal fluid (CSF) alterations. Oligoclonal bands in the CSF were present in 21.8% of patients (67/307) with 12.4% (27/217) of patients presenting OCBs type 2 or 3. 15.8% (49/310) of our cohort revealed signs of blood-brain-barrier (BBB) dysfunction with increased albumin ratios. Mean serum CRP levels were 2.4 mg/l (SD = 9.5). CRP elevation was present in 116/280 cases (41.4%).*Conclusions:* This large retrospective analysis on FEP cohort greatly enriches the clinical data available on this population and contributes to the discussion around inflammation in psychosis. Of note, even though several inflammatory alterations were found both in CSF and in blood tests, we found no evidence for a significant relationship between peripheral inflammation and inflammatory CSF. Furthermore, no significant relationship between CSF alterations and peripheral inflammation measured with CRP could be established.**

Key words: first-episode psychosis/CSF/inflammation/schizophrenia/blood-brain-barrier

Introduction

Based on epidemiological data showing an association between autoimmune and psychotic diseases, the etiology of schizophrenia might be explained at least partially by autoimmune processes.[1] It has been shown that infections and autoimmune processes increase the risk for schizophrenia and affective disorders.[1-4] Neurodegenerative processes develop at least partially as a consequence of inflammatory responses.[5] Multiple lines of evidence from biomarker-driven, post-mortem and neuroimaging studies suggest numerous inflammatory abnormalities in individuals with schizophrenia, including microglial activation and proliferation, pro-inflammatory cytokine upregulation, and abnormal peripheral immune cell counts.[6] C-reactive protein (CRP) is a commonly used biomarker of systemic inflammation worldwide and in a large meta-analysis, CRP levels were moderately increased in people with schizophrenia regardless of the use of antipsychotics and did not change between the first episode of psychosis (FEP) and with progression of schizophrenia (g = 0.66, 95% confidence interval (95% CI) 0.43 to 0.88, P < .001, 24 between-group comparisons, n = 82 962).[7] In a recent prospective follow-up cohort study from Steiner et al, improvement of positive symptoms in schizophrenia after treatment correlated with declining CRP levels (ρ = 0.237, P = .002).[8] Furthermore, meta-analytic evidence shows that the blood-brain-barrier (BBB), which is important for central nervous system (CNS)

homeostasis, is more frequently disrupted in schizophrenia compared to healthy controls,[9] but whether this is a cause or consequence of neurological dysfunction remains unclear.[10] Nevertheless, gross barrier dysfunction is likely to be associated with a disturbance of neural signalling[10] and BBB disruption might be associated with glutamatergic and inflammatory abnormalities which are presumed to be implicated in the etiology of schizophrenia.[10]

Finally, the MRZ reaction (MRZR) composed of the three antibody indices (AI) against measles, rubella and varicella-zoster virus is a sign of an intrathecal immune response. To date, the prevalence of positive MRZR in schizophrenia-spectrum disorders is expected to be low but was only investigated in schizophrenia in one small (n = 39) pilot study.[11]

To date, an evidence base is emerging demonstrating that routine CSF analysis in patients with psychosis does reveal markers of inflammatory or infectious etiology, in addition to the detection of autoimmune encephalitis.[12] This is especially reported in the German national schizophrenia guideline, where a lumbar puncture with subsequent routine CSF analyses is recommended for patients with FEP with signs that could be explained by an underlying somatic condition.[13] Currently, the pathological role of neurotransmitter receptor autoantibodies and their implication in schizophrenia is discussed, since anti-NMDA receptor autoantibodies were detected in serum from ~10% of healthy controls as well as in patients with pure psychotic symptoms.[14]

Regarding CSF outcomes in FEP patients, few studies are available.[15,16] In the largest available cohort of FEP patients from Endres et al, the group of patients with FEP (N=188) showed increased white blood cell (WBC) count in 8/188 patients (4%), elevated albumin quotients (AQs) in 31/188 patients (16%), increased protein concentration in 74/187 patients (40%), increased IgG indices in 4/188 patients (2%), and intrathecal oligoclonal bands (OCBs) in 11/186 patients (6%). OCBs in serum and CSF were detected in 8/186 patients (4%).

No significant differences were found for mean WBC count (P = .644), protein concentration (P = .791), AQ (P = .990), IgG indices (P = .741), or rate of intrathecal OCBs (P = .147) between patients with FEP (N = 188) and patients with recurrent psychosis (N = 267).[15]

Since in at least a subgroup of patients with first-episode psychosis inflammatory processes are presumed to be implicated,[17] we aimed at retrospectively analyzing a cohort of FEP patients with regard to peripheral inflammatory activity (CRP) and standard CSF diagnostics.

Moreover, we aimed at investigating several clinical characteristics, such as drug consumption or the presence of white-matter lesions (WMLs) in MRI scans, which might be linked to a higher rate of peripheral inflammatory activity or CSF alterations.

To the best of our knowledge, our cohort represents the largest available FEP cohort to date about routine CSF diagnostics.

Methods

Data Extraction

This retrospective study was approved by the local ethics committee of the LMU Munich (registration number: 18-570). All inpatients that were admitted at least once in our tertiary care hospital (Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany) with a diagnosis of F2x (schizophrenia-spectrum according to ICD-10) and underwent a lumbar puncture between January 1, 2008 and August 1, 2018 were included. Thus, also patients who initially presented themselves with a drug-induced psychosis (eg cannabis-induced psychosis) and were diagnosed with a diagnosis of F2x within the period of investigation were included in our analyses. Patients with first-episode psychosis were selected after screening of individual patient files of all identified patients. Medical records of all patients were screened and extracted manually by two authors independently (E.W., M.C.) from the electronic clinical documentation system and retrospectively analyzed. As the overall aim was to evaluate the impact of CSF abnormalities in patients that would be in routine be classified as schizophrenia, patients with clinical signs that could indicate the presence of an underlying autoimmune encephalitis (eg seizures, movement disorders, autonomic instability) were excluded based on thorough screening of all available data on clinical and physical examination.

Cerebrospinal Fluid Data and Laboratory Data

All patients underwent a lumbar puncture and basic blood test as part of the clinical routine in the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany. All CSF/serum samples were analyzed in the Institute of Laboratory Medicine, LMU Munich. The CSF analysis included the determination of WBC counts (ref.: ≤5/µl) with pleocytosis defined as >5 cells/µl, total protein levels, albumin in CSF (ref.: ≤0.300 g/l), albumin in serum (ref.: ≤52.0 g/l), IgG indices, and OCBs in serum and CSF. CSF/serum ratios for albumin (Qalb) were adjusted by age according to the formula: $Qalb = (4 + age/15) \times 10^{-3}$, age indicated as years.[18] Detection of oligoclonal IgG bands in CSF and serum was performed on a SEBIA HYDRASYS 2 SCAN FOCUSING semiautomated instrument according to the manufacturer`s instructions, which enables immunofixation and direct detection of OCBs on agarose gels using the HYDRAGEL 9CSF kit (Ref. 4353, Sebia, France). As described in a previous

publication[19] CSF-OCB pattern classification was based on two consensus reports recommendation.[20,21] Five types of patterns were proposed with only patterns 2 and 3 representing intrathecal synthesis of IgG: type 1: normal CSF, type 2: two or more CSF restricted OCB, type 3: CSF restricted OCB and additional, identical OCB in serum and CSF, type 4: identical OCB in CSF and serum, "mirror pattern," type 5: monoclonal bands in CSF and serum. A "mirror pattern" represents systemic immune reaction with passive transfer of oligoclonal bands from the serum to the CSF through an abnormal blood-brain-barrier and does not indicate intrathecal IgG synthesis. Blood serum analysis included the determination of WBC, absolute neutrophil count (ANC), serum albumin levels, serum IgG levels as well as CRP levels. CRP elevation was defined as CRP ≥ 1.0 mg/l as described in a previous meta-analysis.[22] ANC total counts were extracted or—if ANC total counts were missing—calculated based on segmented neutrophils (in %) and WBC data (total in g/l) according to the following formula: ANC [cells/µl] = (segmented neutrophils [%]× total WBC [cells/µl] OR (neutrophils [%]× total WBC [cells/µl].[23] It is to be noted that in the aforementioned formula we did not account for neutrophilic band cells (immature neutrophils), since they were not routinely measured by the laboratory of the LMU Munich. Moreover, neutrophilic band cells usually represent only between 0 and 4% of ANC.[24]

MRI

The MRI protocol was part of the clinical routine and included at least T1-weighted, T2-weighted sequences (1.5 and 3 T scanners). DWI (axial) and FLAIR (coronal) sequences were performed if indicated according to an experienced neuroradiologist. Furthermore, all clinical evaluations of the images were performed by experienced senior physicians in neuroradiology. MRI pathologies were recorded by our colleagues if alterations not common for people in the same age group of the patient were reported. Among MRI pathologies non-specific WML(s) as well as lesions suggestive of multiple sclerosis were recorded.

Statistical Analyses

Analyses were performed using IBM SPSS version 26.0 with a significance level of $\alpha = 0.05$. Distributions of continuous variables were tested for normality with Kolmogorov−Smirnov tests where a violation of the normal distribution was defined as $P < .05$. If the distribution was normal, independent *t*-tests were applied. Mann−Whitney *U* tests were applied in the event of a violation of the normal distribution assumption. Chi-square tests were used to compare differences in categorical variables between groups (two-sided Fisher's exact test was applied for cell count <5 for 2 × 2 tables). The following results to characterize our cohort include many different statistical analyses that were not corrected for multiple testing and must be considered as exploratory.

Results

Characterization of Our Cohort

A total of $n = 687$ FEP patients were admitted to our tertiary care hospital between January 1, 2008 and August 1, 2018. Among them, $n = 314$ (45.7%) FEP patients received a lumbar puncture and were included in our sample. Mean age was 35.1 years (SD = 15.4), with $n = 172$ male (54.8%) and $n = 142$ (45.2%) female patients. No significant differences between FEP patients with or without CSF diagnostics could be found when considering age (mean age FEP without CSF was 35.0 years, SD = 14.1, $Z(1) = -0.540$, $P = .589$) or gender distribution (FEP without CSF $n = 192$ male patients, 51.5%, $X^2(1) = 0.746$, df = 1, $P = .388$). Most patients were diagnosed with schizophrenia according to ICD-10, but all patients were in the schizophrenia-spectrum (F20−29 according to ICD-10) (see table 1). Mean duration of illness was 13.1 months (SD = 25.7). 283 out of 294 patients were treated with at least one antipsychotic (96.3%), mostly with one single antipsychotic (209/294, 71.1%).

Half of the patients (139/277, 50.2%) had a first and/or second-degree relative with a psychiatric disorder. Around a third (107/297, 36%) of all patients were active smokers. Less than a third showed an active drug abuse of at least one substance other than tobacco (27.5%, $n = 84$), with around a fifth of patients (21%, $n = 66$) presenting cannabis consumption with a frequency anywhere from sporadic to daily. Few patients were diagnosed with concurrent neurological disorders (15.7%, $n = 28$) (for a list of neurological comorbidities please see Supplementary Table 1). Some of the patients presented different somatic comorbidities (for a more detailed description please see table 1).

CSF and Serum Characteristics

Mean number of cells was 1.7/µl (SD = 2.0). 3.5% ($n = 11$) showed a pleocytosis. In total, OCBs were measured in CSF in 307 out of 314 patients (97.8%), among this group 217 patients were also tested for OCBs in serum. Oligoclonal bands in the CSF were present in 21.8% of patients ($n = 67/307$). Mean protein level was 38.2 mg/dl (SD = 24.2). Mean albumin levels were 0.25g/l (SD = 0.11). Mean IgG levels were 0.04 g/l (SD = 0.17). Only 1/145 patients (0.7%) showed a positive MRZR. Among patients tested for OCBs both in CSF and Serum, 153 out of 217 (70.5%) patients showed no OCBs (type 1), OCBs type 2 were present in 7/217 patients (3.2%), OCBs

Table 1. Demographic and Clinical Characterization of the Included Patients

Demographics and Clinical Characteristics	Mean	SD	N Total
Age (years)	35.1	15.4	314
	Frequency		*N* Total
Gender (m:f)	172:142	–	314
Diagnosis*	314 (100%)	–	314
Schizophrenia (ICD-10: F20.x)	143/314 (45.5%)	–	314
Schizotypal personality disorder (ICD-10: F21.x)	8/314 (2.5%)	–	314
Persistent delusional disorder (ICD-10: F22.x)	24/314 (7.6%)	–	314
Acute and transient psychotic disorder (ICD-10: F23.x)	73/314 (23.2%)	–	314
Shared psychotic disorder (ICD-10: F24.x)	1/314 (0.3%)	–	314
Schizoaffective disorder (ICD-10: F25.x)	35/314 (11.2%)	–	314
Unspecified nonorganic psychotic disorder (ICD-10: F29.x)	2/314 (0.6%)	–	314
Others**	28/314 (8.9%)	–	314
	Mean	SD	*N* Total
Duration of illness (months)	13.1	25.7	176
	Frequency		*N total*
Positive psychiatric family history***	139/277 (50.2%)	–	277
Antipsychotic treatment	294 (100%)	–	294
None	11/294 (3.7%)	–	294
One AP	209/294 (71.1%)	–	294
Two APs	68/294 (23.1%)	–	294
Three APs	6/294 (2.0%)	–	294
Active smokers	107/297 (36.0%)	–	297
Any neurologic comorbidity****	28/178 (15.7%)	–	178
Active drug abuse*****	84/306 (27.5%)	–	306
Cannabis abuse	66/306 (21.6%)		306
Diabetes type I and II	10/311 (3.2%)	–	311
Cardiovascular condition	45/310 (14.5%)	–	310
Lung condition	20/312 (6.4%)	–	312
Cancer	25/309 (8.1%)	–	309
Active	3/309 (1.0%)	–	309
In remission	22/309 (7.1%)	–	309
Cerebrospinal Fluid	Mean	SD	*N* Total
Number of cells (/µl)	1.7	2.0	314
	Frequency		*N* Total
Pleocytosis >5 cells/µl	11/314 (3.5%)	–	314
	Mean	SD	*N* Total
Albumin (g/l)	0.25	0.11	314
IgG (g/l)	0.04	0.17	313
Oligoclonal bands#	Frequency		*N* Total
No oligoclonal bands, type 1 (*n*/%)	153/217 (70.5%)	–	217
Any oligoclonal bands, type 2 to 5	64/217 (29.5)		217
Oligoclonal bands type 2 (*n*/%)	7/217 (3.2%)	–	217
Oligoclonal bands type 3 (*n*/%)	20/217 (9.2%)	–	217
Oligoclonal bands type 4 (*n*/%)	37/217 (17.1%)	–	217
Oligoclonal bands type 5 (*n*/%)	0/217 (0%)	–	217
	Mean	SD	*N* Total
Protein level (mg/dl)	38.2	24.2	312
	Frequency		*N* Total
positive MRZR (*n*/%)	1/145 (0.7%)	–	145
Serum			
	Mean	SD	*N* Total
WBC (g/l)	6.8	2.2	310
ANC (g/l)##	4.0	1.7	289
Albumin (g/l)	44.8	4.1	313
IgG (g/l)	13.7	59.5	312
	Mean	SD	*N* Total
CRP (mg/l)	2.4	9.5	280

Table 1. Continued

Demographics and Clinical Characteristics	Mean	SD	N Total
	Frequency	–	*N total*
CRP elevation (≥1.0 mg/l)	116/280 (41.4%)	–	280
CSF/serum ratios			
	Mean	SD	N Total
Albumin ratio (CSF/serum)	5.5	2.5	310
	Frequency	–	*N* Total
Elevated albumin ratios	49/310 (15.8%)	–	310
	Mean	SD	*N* Total
IgG ratio (CSF/serum)	2.8	1.9	309
	Frequency		*N* Total
Any CSF alteration###	134/314 (42.7%)	–	314
MRI	Frequency		*N* Total
Any MRI pathologies	118/301 (39.2%)	–	301
White matter lesion(s)	85/301 (28.2%)	–	301
MS suspect lesion(s)	6/301 (2.0%)	–	301

Note: AP, antipsychotic; CRP, c-reactive protein; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MS, multiple sclerosis.
*Diagnosis according to International Statistical Classification of Diseases and Related Health Problems criteria, version 10 (ICD-10).
**Patients that initially presented themselves with psychotic symptoms and a non F2x-diagnosis (eg drug-induced psychosis) and were later diagnosed within the schizophrenia-spectrum.
***For any psychiatric disorder.
****Neurological comorbidities: $n = 28$ (meningitis with epileptic seizure at age of 11 years, meningoencephalitis at 11 years, diabetic polyneuropathy, epilepsy (2×), intracerebral venous anomalia, Morbus Charcot-Marie-Tooth without any symptoms, intracranial hypertension, infantil cerebral palsy, polyneuropathy of unclear origin (2×), migraine (2×), stroke (2×), alcoholic polyneuropathy, traumatic brain injury (5×), weak dorsiflexion of the foot, multiple sclerosis, normal pressure hydrocephalus, polyneuropathy due to vitamin-b12 deficiency, minor stroke, history of neuroborreliosis with ipsilateral facial palsy, history of migraine attacks.
*****Abuse of at least one substance (other than tobacco).
#Five types of OCBs patterns were proposed: type 1 = normal CSF, type 2 = two or more CSF restricted OCB, type 3 = CSF restricted OCB and additional, identical OCB in serum and CSF, type 4 = identical OCB in CSF and serum, "mirror pattern," type 5 = monoclonal bands in CSF and serum.
##If not available, ANC absolute was calculated according to the following formula: ANC [cells/µl] = (segmented neutrophils [%]× total WBC [cells/µl]) OR (neutrophils [%]× total WBC [cells/µl]).
###Any positive OCBs in CSF OR pleocytosis >5 cells/µl OR increased age-adjusted albumin ratio OR positive MRZR.

type 3 were present in 20/217 patients (9.2%), OCBs type 4 were present in 37/217 patients (17.1%) while no OCBs type 5 were found (see table 1). Among patients with positive OCBs type 2, two patients had positive neurological comorbidities (seizures during childhood and migraine). Similarly, among patients with positive OCBs type 3, two patients had positive neurological comorbidities (meningitis with seizures during childhood and Charcot-Marie-Tooth Disease). In total, 42.7% of patients (134/314) showed pathological CSF alterations (increased WBC counts and/or positive OCBs in CSF and/or positive MRZR and/or increased albumin ratios). Overall in our cohort, 15.8% of patients (49/310) revealed signs of BBB dysfunction with increased albumin ratios. Among patients with type 2 or type 3 OCBs, only four (4/27, 14.8%) patients showed neurological comorbidities while another patient (1/27, 3.7%) presented lesions suggesting MS in the MRI. In serum mean CRP levels were 2.4 mg/l (SD = 9.5) with CRP elevation present in 116/280 cases (41.4%) (for a detailed report of other serum variables please see table 1). Mean albumin CSF/serum ratio was 5.5 (SD = 2.5) and mean IgG CSF/serum ratio was 2.8 (SD = 1.9).

MRI Abnormalities

Any MRI pathologies were present in 118 out of 301 cases (39.2%). Non-specific white-matter lesions were detected in around a quarter of all patients (85 out of 301 cases, 28.2%). Lesions suggestive of multiple sclerosis (MS) were present in six cases (2.0%) (see table 1).

Comparisons of CSF Parameters Between Groups With and Without CRP Elevation

No statistically significant difference was found when comparing patients with vs without CRP elevation ($n = 116$ vs $n = 164$) with regard to any CSF alteration ($X^2_{(1)} = 0.155$, df = 1, $P = .694$). No statistically significant difference was found between groups with and without CRP-elevation with regard to IgG ratios ($Z_{(1)} = -0.722$, $P = .470$), albumin ratios ($Z_{(1)} = -1.170$, $P = .242$), CSF cell count ($Z_{(1)} = -1.964$, $P = .050$) and CSF protein

levels ($Z_{(1)} = -0.111$, $P = .911$). No statistically significant difference between these two groups was found with regard to the presence of OCBs type 2 and 3 vs OCBs type 1 ($X^2_{(1)} = 1.516$, df = 1, $p = .218$). No statistically significant difference between these two groups was found with regard to the presence of OCBs type 2 vs OCBs type 3 ($X^2_{(1)} = 0.326$, df = 1, $P = .568$).

Comparisons of CSF Parameters Between Groups With and Without WMLs

No statistically significant difference was found when comparing patients with vs without WMLs ($n = 85$ vs $n = 216$) with regard to any CSF alteration ($X^2_{(1)} = 1.869$, df = 1, $P = 0.172$). No statistically significant difference was found between groups with and without WMLs with regard to IgG ratios ($Z_{(1)} = -0.156$, $P = .876$), albumin ratios ($Z_{(1)} = -0.721$, $P = .471$), CSF cell count ($Z_{(1)} = -1.415$, $P = .157$), CSF protein levels ($Z_{(1)} = -0.377$, $P = .706$) and CRP levels ($Z_{(1)} = -0.966$, $P = .334$). No statistically significant difference between these two groups was found with regard to the presence of OCBs type 2 or 3 vs OCBs type 1 ($X^2_{(1)} = 2.049$, df = 1, $P = .152$). No statistically significant difference between these two groups was found with regard to the presence of OCBs type 2 vs OCBs type 3 ($X^2_{(1)} = 0.964$, df = 1, $P = .326$).

Comparison of Rate of CSF Alterations and Peripheral Inflammation Between Groups With and Without Drug Abuse

A statistically significant difference was found when comparing patients with vs without active drug abuse ($n = 84$ vs $n = 222$) with regard to any CSF alteration ($X^2_{(1)} = 4.033$, df = 1, $P = .045$) with 44/84 (52.4%) patients with drug abuse and 88/222 (39.6%) patients without drug abuse presenting a CSF alteration. No statistically significant differences were found when the aforementioned groups were compared regarding peripheral inflammation measured with CRP ≥1.0 mg/l ($X^2_{(1)} = 0.230$, df = 1, $P = .632$) or with regard to alteration in albumin ratios in CSF ($X^2_{(1)} = 2.721$, df = 1, $P = .099$). No statistically significant difference was found between groups of patients consuming cannabis and patients without drug abuse ($n = 66$ vs $n = 222$) with regard to any CSF alteration ($X^2_{(1)} = 1.504$, df = 1, $P = .220$), regarding altered albumin ratios ($X^2_{(1)} = 1.145$, df = 1, $P = .285$) or regarding peripheral inflammation measured with CRP ≥1.0 mg/l ($X^2_{(1)} = 0.472$, df = 1, $P = .492$). When considering the prevalence of CSF OCBs types 2 and 3, a statistically significant difference was found between patients consuming cannabis and patients without drug abuse ($X^2_{(1)} = 4.347$, df = 1, $P = .037$) with 10 out of 36 patients (27.8%) consuming cannabis being tested positive for OCBs type 2 or 3 vs 16 out of 122 patients (13.1%) without drug abuse being tested positive for the aforementioned OCBs.

Discussion

We present the largest retrospective cohort study on FEP patients with a schizophrenia-spectrum disorder having received CSF diagnostics within the clinical routine in a tertiary care hospital. Most patients (70.5%) showed no oligoclonal bands (OCBs type 1), while a consistent subgroup (17.1%) were of type 4 representing a systemic immune reaction with passive transfer of oligoclonal bands from the serum to the CSF through a disrupted blood-brain-barrier. Among patients with an intrathecal IgG synthesis (OCBs type 2 and 3) only a small percentage exhibited neurological comorbidities or presented MRI lesions suggesting a possible MS diagnosis. Prevalence of OCBs type 2 or 3 in our data (27/217, 12.4%) reflects the previously reported prevalence reported for patients with psychotic symptoms,[15,25] possibly giving credit to the autoimmune hypothesis of schizophrenia. As reported in a recent work,[25] the occurrence of OCBs type 2 or 3 in healthy subjects, though not systematically investigated, is estimated between 0%,[26] 4%,[27] and up to 7%.[28] Given the significant genetic overlap between inflammatory conditions and psychiatric disorders,[29] it could perhaps be speculated that the aforementioned higher prevalence of OCBs type 2 and 3 in FEP patients compared to the general population might suggest the presence of a FEP subgroup with an inflammatory etiology of the disease. Epidemiological data did not show a high rate of pleocytosis with >5 cells/µl (3.5%, 11/314), nor an intrathecal synthesis of specific IgG antibodies against viruses of measles, rubella and zoster (MRZR positive in 1/145 patients, 0.7%). A substantial subgroup of patients (15.8%, 49/310) showed signs of BBB dysfunction with increased albumin ratios, possibly explaining the similar rate of OCBs type 4 and suggesting a transfer of OCBs between the periphery and the CNS. Our results appear to be in line with previous studies investigating FEP samples.[15,30] Interestingly, we found that the prevalence of OCBs type 2 or 3 in FEP patients who consume cannabis (27.8%) was more than double that of patients without drug abuse (13.1%) or that of our sample overall (12.4%). Moreover, patients with cannabis abuse did not significantly differ from patients without drug abuse with regard to albumin ratio as a proxy for BBB breakdown or with regard to CRP elevation as a proxy for peripheral inflammation. One may speculate that cannabis abuse is associated with a central neuroinflammatory process while it does not appear to be associated with BBB disruption or peripheral inflammation. In the scientific literature, an increased risk of schizophrenia has been shown to be associated with autoimmune diseases.[2,31] Furthermore,

severe infections are also correlated with a higher risk of developing schizophrenia, with the risk increasing with the temporal proximity of the infection.[2] The inflammation resulting from autoimmune or infectious diseases might increase the permeability of the BBB, thus exposing CNS tissues to molecules such as cytokines or antibodies and hence possibly increasing the chance of activation of resident inflammatory cells.[32] Since we could not show a BBB disorder in patients with cannabis abuse, it remains unclear whether our incidental finding of increased intrathecal IgG production among cannabis users with psychotic symptoms is cause or consequence of cannabis intake. Considering substance abuse at large, thus including alcohol and other psychotropic substances, more than half of the patients with drug abuse (44/84, 52.4%) presented CSF alterations while only 39.6% (88/222) of patients without drug abuse showed alterations of the CSF.

Noteworthy, overall CSF alterations comprising at least positive OCBs in CSF or pathological CSF values (pleocytosis, increased age-corrected albumin ratio or positive MRZ reaction) were present in 134/314 (42.7%) of the population. Moreover, even though peripheral CRP alteration was present in 116/280 cases (41.4%), we found no evidence for a significant association between CSF alterations and peripheral inflammation. It has to be noted that the reasons for this lack of correlation could be multiple and difficult to address in a retrospective study. Furthermore, it might be speculated that assessment of CRP levels without the measurement of inflammatory cytokines implicated in both peripheral and CNS inflammation[33] could have blunted the sensitivity of detecting inflammatory processes in patients. Moreover, no significant relationship between the emergence of WMLs, CSF alterations and peripheral inflammation (measured with CRP) could be established. Considering MRI data, we found abnormalities in 39.2% of our cohort. This is substantially lower than previously reported by Endres et al[15] who found MRI abnormalities in 72% of patients, although analyses were not restricted to FEP. Similarly, WMLs were found in 28.2% of MRI scans, while in the aforementioned publication WMLs were reported in 42% of patients. As a reference point, WMLs in healthy adults with a similar mean age have been reported to be around 5.3%.[34] As limitation, it must be noted that our approach was retrospective and did not take into account follow-up data, thus the question if the observed CSF alterations among FEP are cause or consequence of the disease remains elusive. Furthermore, CRP and ANC were not controlled for potential confounders (such as body-mass index, age, smoking status). Next, our results were not corrected for multiple testing. Thus, our reported significant effects must be considered as exploratory and confirmed in independent samples. However, most of our findings were descriptive based on the largest FEP-CSF cohort to date and allow for a general overview of the relationship between CSF abnormalities and inflammatory factors in FEP. Finally, it should be mentioned that patients included in our sample were admitted in a tertiary care hospital and as such might not be fully representative of FEP patients in general. Moreover, among the 687 FEP patients admitted to our hospital only 45.7% ($n = 314$) received a lumbar puncture as part of the clinical routine. However, given the size of our sample and the fact that our hospital has a medical supply mandate for a large part of Munich with its more than 1.3 million inhabitants as well as the demographical homogeneity of the two groups (FEP patients with and without subsequent CSF diagnostics) allow us to speculate that our findings might be generalized to other areas of the healthcare sector and that the results of this study could be representative of an unselected FEP population. Reasons for not having received CSF diagnostics could be multiple and remain elusive. Besides patients declining to receive a lumbar puncture, other reasons for not receiving CSF diagnostics could be leaving the hospital against medical advice or a rapid remittent course of the psychotic symptoms after initiation of antipsychotic treatment. Nevertheless, this study further contributes to the knowledge on the prevalence of CSF alterations in FEP. Prospective studies are needed with an assessment of cognitive impairment and symptom severity in addition to CSF diagnostics beyond the clinical routine to foster the evidence with regard to the prevalence of neuroinflammatory processes in the CNS and their clinical implication in FEP.

Summary of Inflammatory Findings

To summarize the findings regarding inflammation, we report 12.4% of our cohort presenting OCBs type 2 or 3, thus suggesting an intrathecal IgG production in a substantial subgroup of FEP patients. The prevalence of OCBs type 2 or 3 was higher (13.1%) in patients consuming drugs and more than double (27.8%) in patients consuming cannabis. Looking at BBB dysfunction measured by CSF/serum albumin ratios, 15.8% of our cohort presented an altered ratio. Such a BBB alteration could explain the passive transfer of oligoclonal bands from the serum to the CSF accounting for the 17.1% of FEP patients presenting OCBs type 4. Finally, no significant relationship between peripheral inflammation and inflammatory CSF was found, potentially implying the presence of a FEP subgroup with an intrathecal inflammatory etiology of the disease.

Conclusion

This large retrospective analysis of a FEP cohort largely contributes to the clinical data available on this population as well as to the discussion around inflammation in psychosis. In this study we found no evidence for a significant

relationship between peripheral inflammation and inflammatory CSF, nevertheless several inflammatory alterations were found both in CSF and in blood tests. When considering the prevalence of OCBs type 2 and 3, FEP patients in our cohort showed values like those reported in previous studies, which were markedly higher than values found in the general population, thus potentially implying the presence of a FEP sub-group with an inflammatory etiology of the disease. Interestingly a markedly greater prevalence of OCBs type 2 and 3 was found in patients with cannabis abuse. Finally, no significant relationship between the emergence of WMLs, CSF alterations and peripheral inflammation measured with CRP could be established.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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References

1. Cullen AE, Holmes S, Pollak TA, et al. Associations between non-neurological autoimmune disorders and psychosis: a meta-analysis. *Biol Psychiatry.* 2019;85(1):35–48.
2. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. *JAMA Psychiatry* 2013/8 2013;70(8):812–820.
3. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar Disord.* 2010;12(6):638–646.
4. Wium-Andersen MK, Ørsted DD, Nordestgaard BG. Elevated C-reactive protein and late-onset bipolar disorder in 78 809 individuals from the general population. *Br J Psychiatry.* 2016;208(2):138–145.
5. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science.* 2016;353(6301):777–783.
6. Najjar S, Pahlajani S, De Sanctis V, Stern JNH, Najjar A, Chong D. Neurovascular unit dysfunction and blood-brain barrier hyperpermeability contribute to schizophrenia neurobiology: a theoretical integration of clinical and experimental evidence. *Front Psychiatry.* 2017;8:83.
7. Fernandes BS, Steiner J, Bernstein HG, et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Mol Psychiatry.* 2016;21(4):554–564.
8. Steiner J, Frodl T, Schiltz K, et al. Innate immune cells and C-reactive protein in acute first-episode psychosis and schizophrenia: relationship to psychopathology and treatment. *Schizophr Bull.* 2020;46(2):363–373.
9. Orlovska-Waast S, Köhler-Forsberg O, Brix SW, et al. Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. *Mol Psychiatry.* 2019;24(6):869–887.
10. Pollak TA, Drndarski S, Stone JM, David AS, McGuire P, Abbott NJ. The blood-brain barrier in psychosis. *Lancet Psychiatry.* 2018;5(1):79–92.
11. Endres D, Huzly D, Dersch R, et al. Do patients with schizophreniform and bipolar disorders show an intrathecal, polyspecific, antiviral immune response? A pilot study. *Fluids Barriers CNS.* 2017;14(1):34.
12. Pollak TA, Lennox BR. Time for a change of practice: the real-world value of testing for neuronal autoantibodies in acute first-episode psychosis. *BJPsych Open.* 2018;4(4):262–264.
13. Hasan A, Falkai P, Lehmann I, Gaebel W. Schizophrenia. *Dtsch Arztebl Int.* 2020;117(24):412–419.
14. Hammer C, Stepniak B, Schneider A, et al. Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. *Mol Psychiatry.* 2014;19(10):1143–1149.
15. Endres D, Meixensberger S, Dersch R, et al. Cerebrospinal fluid, antineuronal autoantibody, EEG, and MRI findings from 992 patients with schizophreniform and affective psychosis. *Transl Psychiatry.* 2020;10(1):279.
16. Kranaster L, Koethe D, Hoyer C, Meyer-Lindenberg A, Leweke FM. Cerebrospinal fluid diagnostics in first-episode schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* 2011;261(7):529–530.
17. Pillinger T, Osimo EF, Brugger S, Mondelli V, McCutcheon RA, Howes OD. A Meta-analysis of immune parameters, variability, and assessment of modal distribution in psychosis and test of the immune subgroup hypothesis. *Schizophr Bull.* 2019;45(5):1120–1133.
18. Trendelenburg C. Labormedizinische Spezialbefundung und ärztliche Verantwortung. *J Lab Med.* 1994;18(12):545–551.
19. Bernitsas E, Khan O, Razmjou S, et al. Cerebrospinal fluid humoral immunity in the differential diagnosis of multiple sclerosis. *PLoS One.* 2017;12(7):e0181431.
20. Andersson M, Alvarez-Cermeño J, Bernardi G, et al. Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. *J Neurol Neurosurg Psychiatry.* 1994;57(8):897–902.
21. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol.* 2005;62(6):865–870.

22. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychol Med.* 2019;49(12):1958–1970.
23. Coates TD. Approach to the patient with neutrophilia. *Up To Date* 2021.
24. Jameson JL KD, eds. *Chapter 60: Disorders of Granulocytes and Monocytes*. 20th ed. Harrison's Principles of Internal Medicine; 2018.
25. Rattay TW, Martin P, Vittore D, et al. Cerebrospinal fluid findings in patients with psychotic symptoms-a retrospective analysis. *Sci Rep.* 2021;11(1):7169.
26. Blennow K, Fredman P, Wallin A, et al. Protein analysis in cerebrospinal fluid. III. Relation to blood-cerebrospinal fluid barrier function for formulas for quantitative determination of intrathecal IgG production. *Eur Neurol.* 1993;33(2):134–142.
27. Haghighi S, Andersen O, Rosengren L, Bergström T, Wahlström J, Nilsson S. Incidence of CSF abnormalities in siblings of multiple sclerosis patients and unrelated controls. *J Neurol.* 2000;247(8):616–622.
28. Zeman AZ, Keir G, Luxton R, Thompson EJ. Serum oligoclonal IgG is a common and persistent finding in multiple sclerosis, and has a systemic source. *QJM.* 1996;89(3):187–193.
29. Andreassen OA, Harbo HF, Wang Y, et al. Genetic pleiotropy between multiple sclerosis and schizophrenia but not bipolar disorder: differential involvement of immune-related gene loci. *Mol Psychiatry* 2015;20(2):207–214.
30. Bechter K, Reiber H, Herzog S, Fuchs D, Tumani H, Maxeiner HG. Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: identification of subgroups with immune responses and blood-CSF barrier dysfunction. *J Psychiatr Res.* 2010;44(5):321–330.
31. Eaton WW, Byrne M, Ewald H, et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. *Am J Psychiatry.* 2006;163(3):521–528.
32. Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? Maybe it's the antibodies. *Nat Rev Immunol.* 2009;9(6):449–456.
33. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci.* 2008;9(1):46–56.
34. Hopkins RO, Beck CJ, Burnett DL, Weaver LK, Victoroff J, Bigler ED. Prevalence of white matter hyperintensities in a young healthy population. *J Neuroimaging.* 2006;16(3): 243–251.