Comprehensive Psychiatry 102 (2020) 152196

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Increased IL-8 concentrations in the cerebrospinal fluid of patients with unipolar depression

Hanna Kuzior [a,b], Bernd L. Fiebich [b], Nizar M. Yousif [b], Soraya W. Saliba [b], Christiane Ziegler [b], Kathrin Nickel [a,b], Simon J. Maier [a,b], Patrick Süß [c], Kimon Runge [a,b], Miriam Matysik [a,b], Rick Dersch [d], Benjamin Berger [d], Tilman Robinson [d], Nils Venhoff [e], Franziska Kessler [f], Thomas Blank [f], Katharina Domschke [b,g], Ludger Tebartz van Elst [a,b], Dominique Endres [a,b,*]

[a] Section for Experimental Neuropsychiatry, Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[b] Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[c] Department of Molecular Neurology, University Hospital Erlangen, Erlangen, Germany
[d] Department for Neurology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[e] Department of Rheumatology and Clinical Immunology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[f] Institute of Neuropathology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[g] Center for Basics in Neuromodulation, Faculty of Medicine, University of Freiburg, Germany

ARTICLE INFO

Keywords:
Interleukin 8
IL-8
Depression
Neuroinflammation

ABSTRACT

Introduction: Unipolar depression is a common and debilitating disorder. Immunological explanatory approaches have become increasingly important in recent years and can be studied particularly well in the cerebrospinal fluid (CSF). Previous studies discerned alterations in interleukin (IL)-6 and IL-8 levels; however, findings regarding IL-8 were partly contradictory. The aim of the present study was to investigate the concentrations of different cytokines and chemokines, focusing on IL-8, in the CSF of patients with unipolar depression.
Materials and methods: Participants included 40 patients with unipolar depression and 39 mentally healthy controls with idiopathic intracranial hypertension. CSF cytokine levels were measured using a magnetic bead multiplexing immunoassay.
Results: IL-8 levels in the CSF of the patient group with depression were significantly higher than those in the control group (Mean ± SD: 38.44 ± 6.26 pg/ml versus 21.40 ± 7.96 pg/ml; $p < .001$).
Limitations: The significance of the results is limited by the retrospective design and methodological aspects.
Discussion: The main findings of this study were significantly higher concentrations of IL-8 in the CSF of patients with unipolar depression than in the control group. The detection of high CSF IL-8 levels in this study supports the idea that inflammatory processes might play a role in the pathophysiology of a subgroup of patients with depression.

1. Introduction

Depression is a common and debilitating disorder that affects millions of people across all ages and cultures [14,19]. Patients suffer from lack of motivation, loss of interest and pleasure, depressed mood, and suicidal tendencies [3]. Evidence supporting involvement of an inflammatory component and immune processes in the development of depression has accumulated over the last decade [26,27].

Our study group has previously published case reports of patients with Hashimoto encephalopathy presenting as major depression who underwent remission after successful treatment with immunomodulatory treatment [11,28]. Building on these findings, our working group investigated the cerebrospinal fluid (CSF) of 125 patients with unipolar depression and found clear signs of inflammation, including CSF pleocytosis in 4% and oligoclonal bands (OCBs) in 6.5% of patients, as well as nonspecific signs for potential neuroinflammatory processes with blood-brain-barrier (BBB) dysfunction (i.e., increased age-dependent albumin quotients [AQs]) in 19.4% of all patients [10].

In line with these findings, it has been hypothesized that increased secretion of pro-inflammatory cytokines by activated leukocytes is associated with depressive symptoms. Cytokines are inflammatory mediators that regulate inflammatory reactions and enable the communication of the immune system with the central nervous system (CNS). It has been shown that cytokines can both cross the BBB and be produced inside the brain by neurons, astrocytes, and microglial cells.

* Corresponding author at: Section for Experimental Neuropsychiatry, Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany.
E-mail address: dominique.endres@uniklinik-freiburg.de (D. Endres).

https://doi.org/10.1016/j.comppsych.2020.152196

They can influence the metabolism of neurotransmitters, thus affecting behavior as well as emotion [7,26,34]. Recent meta-analyses have shown that depressed patients have high concentrations of pro-inflammatory cytokines, especially interleukins (IL) such IL-1 and IL-6, in their blood [8,16]. However, the number of studies measuring cytokines in the CSF of psychiatric patients is limited. Table 1 summarizes all case-control studies on pro-inflammatory cytokines in the CSF of depressed patients.

1.1. Rationale of this study

The aim of this study was to investigate the concentrations of different cytokines and chemokines in the CSF of a group of patients with unipolar depression and a group of age-matched controls to explore signs of increased pro-inflammatory activity in the CNS. Investigation of the CSF plays an important role in current neuropsychiatric research as earlier studies have been able to show different concentrations of cytokines in the CNS and in the blood of different phenotypes (patients with infectious and autoimmune neuroinflammation, headaches, affective and schizophreniform disorders; [25]). Therefore, examination of CSF for pro-inflammatory markers may provide insights into intrathecal inflammatory processes. Based on earlier findings from routine CSF diagnostics showing immunological alterations and several reports of altered and partly contradictory results of proinflammatory IL concentrations (especially with regard to IL-8 levels) in the CSF of patients with depression, the detection of increased IL-8 levels in the depression group was predicted. For the subgroup of patients exhibiting increased levels of all detectable pro-inflammatory cytokines, it was aimed to characterize the patterns of their clinical, laboratory, and instrument-based findings in detail. Moreover, an exploratory correlation analysis of the relationship among cytokines/chemokines, CSF basic parameters, thyroid values, and different psychometric scores was performed.

2. Participants and methods

The study was part of a larger project that was approved by the local ethics committee (Faculty of Medicine, Freiburg University, EK-Fr 609/14). All patients gave their written informed consent before the lumbar puncture. The control subjects were subsequently contacted and were asked about their agreement to participate in the study.

2.1. Patient group

The patient group included patients with unipolar depressive syndromes undergoing lumbar puncture at the Department of Psychiatry and Psychotherapy of the Medical Center – University of Freiburg to exclude organic causes of the depressive syndrome. From the group of patients with depression, which was created for a larger CSF project, the youngest patients were selected to achieve an age matching with the control group. A diagnosis of depression was made by experienced senior psychiatrists according to the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10; https://apps.who.int/iris/handle/10665/37108). Patients with neurodegenerative disorders (e.g., mild cognitive impairment [ICD-10: F06.7] or dementia [ICD-10: F03]), developmental disorders (e.g., ADHD [ICD-10: F90.x]), schizophreniform disorders (ICD-10: F2.X), bipolar disorders (ICD-10: F31.X), alcohol abuse or dependence (ICD-10: F10.1/2), substance dependence (ICD-10: F1x.2; except for nicotine [F17.2]), all neurological diseases, and immunological disorders with frequent brain involvement (e.g., systemic lupus erythematosus) were excluded from the study. Presence of peripheral immunological disorders without clear brain involvement such as Hashimoto's thyroiditis did not lead to exclusion. Clinical and demographic data of the patients were extracted from patient discharge reports. Psychometric scores were collected within the framework of basic clinical diagnostics. This included number of suicide attempts, previous inpatient stays, Clinical Global Impression (CGI) scores [5] and Global Assessment of Functioning (GAF) scores [32,45]. Patients also underwent cerebral magnetic resonance imaging (cMRI) and electroencephalographies (EEGs). cMRI results were analyzed by experienced neuroradiology specialists from the local clinic of neuroradiology and EEGs were evaluated by the responsible physicians.

2.2. Control group

The control group consisted of 39 mentally healthy controls with idiopathic intracranial hypertension (ICD-10 G93.2), a benign, non-primarily inflammatory chronic condition. All controls with idiopathic intracranial hypertension with clearly identifiable secondary forms of intracranial hypertension (e.g., due to sinus vein thrombosis), previously known psychiatric or neurological disorders (with the exception of headache), and treatment with psychotropic drugs were also excluded. Participants with immunological disorders with frequent brain involvement were also excluded from the control group, whereas presence of peripheral immunological disorders without clear brain involvement did not lead to exclusion from the control group. Recruitment of patients with idiopathic intracranial hypertension as control groups was established in previous CSF studies (e.g., [41]).

2.3. CSF storage and analyses

CSF samples were stored at −80 °C after lumbar puncture. All routine CSF tests were carried out in the CSF laboratory of the University Medical Center Freiburg as described previously [9,12]. CSF cytokine levels were measured using the Human Cytokine Magnetic 30-Plex Panel (ThermoFisher, Waltham, MA), a magnetic-bead multiplex immunoassay, and the MAGPIX® machine (ThermoFisher, Waltham, MA) for reading and analyzing the assay. The panel was used in accordance with the manufacturer's specifications with the exception that this panel was not established for the analysis of CSF in advance. To determine whether the calculated concentrations of the individual cytokines were reliable, the mean fluorescent intensity after deduction of the blank value was investigated, known as the net median fluorescence intensity (NetMFI), as well as the number of magnetic beads measured per analyte per well (bead count). In the present study, all values with a NetMFI below the lowest standard of the standard curve of the respective cytokine and with a bead count below 20 were excluded. Only samples that were measurable (and therefore not below the detection level) in >50% of the samples were analyzed. Cytokine/chemokine concentrations below the detection level were set to zero.

2.4. Data handling and statistical analyses

All statistical analyses were performed using Statistical Package for the Social Sciences, version 24 (IBM Corp., Armonk, NY). Group comparisons for categorical variables (e.g., gender) were carried out using Pearson's chi-squared test. Group comparisons for different continuous variables (age, CSF basic findings) were performed using two-sided independent-sample *t*-tests. The significance level was set to *p*-values of <0.05. For group comparisons of cytokines/chemokines, the assumption of normality for parametric tests was tested using a Kolmogorow-Smirnow test. The assumption of normality was violated for IFN-α and IP-10. Therefore, we applied a non-parametric Mann-Whitney *U* test for independent samples. A Bonferroni correction for multiple testing was performed, which led to a corrected *p*-value significance threshold of <0.0125 (for four measurable cytokines). The subgroup analyses for cytokines/chemokines were also performed with a non-parametric Mann-Whitney U test for independent samples. The role of potential influencing factors was analyzed using two analyses of variance (ANOVAs) with 1) gender (and interaction with group), and 2) psychotropic medication (including selective serotonin reuptake inhibitors [SSRIs], selective serotonin/noradrenaline reuptake inhibitors [SSNRIs],

Table 1
Case-control studies analyzing cytokines in the CSF of depressed patients (meta-analyzed in [29]).

	Cohorts (Average age in years)	Cytokines measured (Method)	Results
[6]	$N = 18$ depression (38.3) $N = 12$ controls (32.7)	IL-6 (ELISA)	No difference in IL-6
[21]	$N = 32$ depression (39) $N = 47$ controls (37)	IL-1β, IL-6, IL-8, TNF-α (ELISA)	High IL-6
[24]	$N = 18$ depression (40.4) $N = 25$ controls (29.9)	IL-1, IL-6, TNF-α (ELISA)	No difference in IL-1, IL-6, TNF-α
[36]	$N = 30$ depression (42.7) $N = 35$ controls (41.3)	IL-6 (ELISA)	High IL-6
[18]	$N = 19$ depression (72.8) $N = 67$ controls (72.4)	IL-6, IL-8 (Multiplex Assay)	High IL-6 and IL-8
[17]	$N = 71$ depression* (38) $N = 48$ controls (38)	IL-8 (Ultra-sensitive electrochemiluminescence-based immunoassay)	Low IL-8

* 19 patients were diagnosed with dysthymia. Abbreviations: IL = Interleukin, TNF = Tumor Necrosis Factor, ELISA = Enzyme Linked Immunosorbent Assay.

tricyclic antidepressants, bupropion, mirtazapine, typical neuroleptics, atypical neuroleptics, and mood stabilizers) as random factors. A Spearman's rank correlation was performed to test for the relation between cytokines/chemokines and CSF basic parameters (white blood cell count, total protein, AQs, and immunoglobulin G index), thyroid values (thyroid stimulating hormone, L-thyroxine, and triiodothyronine), and different psychometric scores (GAF/CGI score and number of suicide attempts/previous inpatient stays) in the patient group. No correction for multiple testing was performed in the correlation analysis due to the exploratory nature of these calculations. Therefore, significance was set at $p < .05$ for these analyses. The profiles of all patients with conspicuous cytokine profiles in all measurable pro-inflammatory cytokines (i.e., at least one standard deviation above the mean levels of the patient group) were characterized in detail.

3. Results

3.1. Demographic data

The study cohorts consisted of 40 patients with depressive syndromes and 39 mentally healthy controls. Those in the patient group were between 18 and 47 years of age (Mean ± SD: 32.9 ± 7.9 years), and those in the control group were between 18 and 61 years of age (Mean ± SD: 34.6 ± 12.0 years). There was no significant difference in age ($p = .458$). There was, however, a significant difference in gender ratio (15 males and 25 females in the patient group vs. 6 males and 33 females in the control group, $p = .026$).

All those in the patient group suffered from severe depressive episodes, the majority (82.5%) without accompanying psychotic symptoms. Of the 40 patients, 27 (67.5%) had recurrent or chronic depression. Twenty-nine (72.5%) patients had a positive family history of psychiatric disorders. The majority of patients with unipolar depression (95%) were treated with psychotropic drugs at the time of lumbar puncture, most commonly SSNRIs. Eleven (27.5%) patients had at least one psychiatric comorbidity. All clinical and demographic data of patients and controls is summarized in Tables 2 and 3.

3.2. Basic CSF findings and instrumental diagnostics

Significantly higher rates of BBB dysfunction were found in patients compared to control subjects. Fifteen patients (37.5%) showed increased total proteins, and 8 patients (20%) showed increased levels of age-dependent AQs. Furthermore, CSF-specific OCBs were found in two patients (5%) but not in any of the control subjects. All CSF findings are summarized in Table 4. Of the 40 patients, 24 (66.6%) had abnormal cMRI scans. The majority of alterations were white matter (WM) lesions and signs of microangiopathy (41.6%). The patients with WM lesions and microangiopathy were significantly older (36 ± 6.6 years versus 30.6 ± 7.7 years) than the patients without lesions ($p = .034$). Two patients (5.1%) had pathological EEGs. The cMRI and EEG findings are presented in Table 5.

Table 2
Clinical data of patients and controls.

	Patients ($N = 40$)	Controls ($N = 39$)	Statistics
Gender	15 M: 25 F	6 M: 33 F	$p = .026$
Average age at the time of sampling (age range)	32.9 ± 7.9 (18–47 years)	34.6 ± 12.0 (18–61 years)	$p = .458$
Diagnosis			
Severe depressive episode	$N = 40$	-	
With psychotic symptoms	$N = 7$	-	
Without psychotic symptoms	$N = 33$	-	
Number of previous inpatient stays and suicide attempts			
Number of inpatient stays	16 × no pre-stays, 12 × 1 stay, 6 × 2 stays, 2 × 3 stays, 1 × 4 stays, 2 × 5 stays, 1 × 6 stays		
Number of suicide attempts	34 × 0 attempts, 3 × 1 attempt, 2 × 2 attempts, 1 × 6 attempts	-	
Psychiatric comorbidity			
OCD	$N = 3$	-	
Anxiety disorder	$N = 2$	-	
Eating disorder	$N = 2$	-	
Dysthymia	$N = 4$	-	
Others	$N = 2$*	-	
Available diagnostic tests			
CSF	$N = 40$	$N = 39$	
cMRI	$N = 36$	Not analyzed	
EEG	$N = 39$	Not analyzed	
Psychotropic drugs at the time of sampling			
SSRI	$N = 10$	-	
SSNRI	$N = 21$	-	
Tricyclic antidepressants	$N = 8$	-	
Bupropion	$N = 4$	-	
Mirtazapine	$N = 7$	-	
Typical neuroleptics	$N = 4$	-	
Atypical neuroleptics	$N = 21$	-	
Lithium	$N = 9$	-	
Anticonvulsant	$N = 1$	-	

* Borderline personality disorder, Conversion disorder. Abbreviations: OCD = obsessive compulsive disorder, CSF = cerebrospinal fluid, cMRI = cerebral magnetic resonance imaging, EEG = electroencephalography, F = female, M = male, SSRI = selective serotonin reuptake inhibitor, SSNRI = selective serotonin/noradrenaline reuptake inhibitor.

Table 3
Demographic data. Not documented in the control group.

	Patients with depression ($N = 40$)
Marital status	
Single	31 (77.5%)
Married	7 (17.5%)
Divorced	2 (5%)
Level of education	
Low	2 (5%)
Middle	8 (20%)
High	29 (72.5%)
Unknown	1 (2.5%)
Work situation	
Unemployed	6 (15%)
Working	21(52.5%)
In training	11 (27.5%)
Retired	1 (2.5%)
Housewife/−man	1 (2.5%)
Housing situation	
Alone	18 (45%)
With partner/family	11 (27.5%)
With parents/guardian	10 (25%)
Unknown	1 (2.5%)

Table 5
cMRI and EEG pathologies in the patient group.

Localization of cMRI lesions	Patients ($N = 36$)
White matter/cerebral microangiopathy	15 (41.6%)*
Generalized/localized cortical atrophy	–
Post-ischemic changes	–
Other pathologies	
Unspecific brain stem signal changes	1 (2.7%)**
Anatomical variants***	8 (22.2%)
Total cMRI pathologies	24/36 patients (66.6%)
EEG pathologies	Patients ($N = 39$)
Continuous generalized slow activity	1/39 (2.5%)
Continuous regional slow activity	–
Intermittent regional/generalized slow activity	–
Epileptic activity	1/39 (2.5%)
Total EEG pathologies	2/39 patients (5.1%)

* Already the presence of a single white matter lesion was coded as positive.
** Nonspecific signal changes on both sides point to unclear etiology, not typical for dilated perivascular spaces, possibly post-inflammatory; otherwise inconspicuous intracranial findings.
*** Cysts, asymmetries, malrotations, AV-malformations. Abbreviations: cMRI = cerebral magnetic resonance imaging, EEG = electroencephalography.

3.3. Cytokine/chemokine findings

The authors were able to determine levels of monocyte chemoattractant protein 1 (MCP-1), interferon alpha (IFN-α), interferon gamma-induced protein 10 (IP-10), and IL-8. The MCP-1 results for one sample and the IP-10 results for one sample were below the detection level. For IFN-α, results of 21 samples were below the detection level, and for IL-8, the results from all samples were measurable. IL-6 levels were not measurable in the CSF of more than 50% of patients with depression and controls combined, and therefore, IL-6 levels were not included in the analysis and do not appear in Table 6. IL-8 concentrations in the CSF of the patient group were significantly higher than concentrations in the control group ($p < .001$; Table 6, Fig. 1). The patient and control groups did not differ significantly from each other with regard to MCP-1, IFN-α, and IP-10 concentrations (Table 6). There were no significant differences in IL-8 levels between patients without ($N = 33$) and with ($N = 7$) psychotic symptoms ($p = .095$). There also were no significant differences in IL-8 concentrations between patients with a first depressive episode ($N = 13$) and recurrent or chronic depression ($N = 27$; $p = .568$).

3.4. Effects of possibly confounding factors

The first ANOVA with the random factor gender still resulted in significant IL-8 group effects ($F(1,75) = 465.5$, $p = .029$). There was no significant gender effect and no group interaction. In the second ANOVA, corrected for the potential influence of psychotropic medication, the IL-8 levels still showed a significant group difference ($F(1,69) = 40.2$, $p < .001$). None of the psychotropic medications had a significant effect on IL-8 levels.

Table 6
Results of the cytokine multiplex assay.

	Patients ($N = 40$)	Controls ($N = 39$)	Statistics*
MCP-1 (Mean ± SD)	197.08 ± 51.37 pg/ml	182.27 ± 86.71 pg/ml	$p = .112$
IFN-α (Mean ± SD)	7.95 ± 8.68 pg/ml	11.24 ± 5.21 pg/ml	$p = .074$
IP-10 (Mean ± SD)	10.00 ± 8.30 pg/ml	9.94 ± 9.69 pg/ml	$p = .754$
IL-8 (Mean ± SD)	38.44 ± 6.26 pg/ml	21.40 ± 7.96 pg/ml	$\mathbf{p < .001}$

* Significance level after Bonferroni correction for multiple testing: $p < .0125$. Abbreviations: SD = standard deviation MCP = Monocyte Chemoattractant Protein, IFN- α = Interferon alpha, IP = Interferon-γ-induced Protein, IL = Interleukin.

3.5. Characteristics of patients with major depression and increased CSF cytokine concentrations

Two outlier patients with increased concentrations of all measurable pro-inflammatory CSF cytokines were detected. The first case (Case 1) was a mid-40-year-old male patient with a hypochondriac, recurrent severe depressive disorder. This patient showed high CSF

Table 4
Findings in CSF basic diagnostics. Thresholds according to [40].*, **

	Patients ($N = 40$)	Controls** ($N = 39$)	Statistics
White blood cell count/μl (Mean ± SD)	1.88 ± 1.27	2.60 ± 7.59* ($N = 35$)	$p = .553$
Increased white blood cell counts (reference ≤5/μl)	2 (5%)	1* (2.9%; $N = 35$)	$p = .637$
Total protein in mg/l (Mean ± SD)	419.93 ± 151.84	309.33 ± 142.5	$\mathbf{p = .001}$
Number of patients with increased total protein (reference ≤450 mg/l)	15 (37.5%)	6 (15.4%)	$\mathbf{p = .026}$
Albumin quotient (Mean ± SD)	5.13 ± 2.02	3.93 ± 1.81	$\mathbf{p = .007}$
Number of patients with increased AQs (references: <40y.: 6.5×10^{-3}; 40-60y.: 8×10^{-3}; >60y.: 9.3×10^{-3})	8 (20%)	2 (5.1%)	$\mathbf{p = .047}$
IgG index (Mean ± SD)	0.49 ± 0.09	0.50 ± 0.038	$p = .309$
Number of patients with increased IgG index (≤0.7)	1 (2.5%)	0 (0%)	$p = .320$
CSF specific OCBs	2 (5%)	0 (0%; $N = 38$)	$p = .163$

* One of the controls suffered from reactive pleocytosis (46 cells /μl), which regressed independently to normal WBC counts. The magnetic resonance imaging was normal in this patient. No other cause fort the transient, self-limiting pleocytosis was detected, therefore it was interpreted as reactive pleocytosis.
** Overall, 7 of 39 controls (18%) showed alterations in this control group of patients with idiopathic intracranial hypertension. Abbreviations: WBC = white blood cell, SD = standard deviation, y. = years, AQs, albumin quotients, IgG = immunoglobulin G, OCBs = oligoclonal bands.

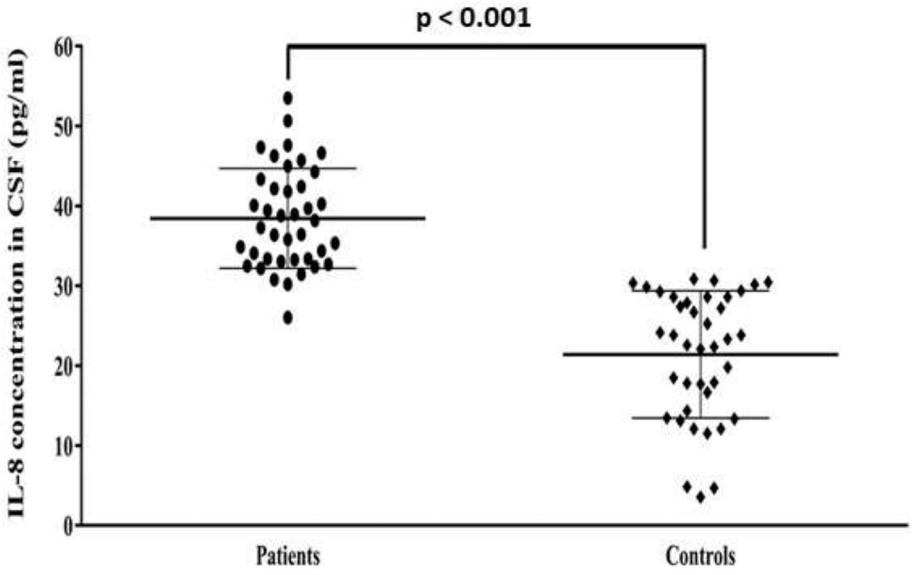

Fig. 1. IL-8 concentrations in cerebrospinal fluid of depressed patients and controls (mean values ± standard deviations).

concentrations of IL-8, MCP-1, IP-10, and IFN-α. The basic CSF diagnostic showed slightly increased total protein (461 mg/l; reference ≤450 mg/l) and one CSF-specific OCB. Unfortunately, additional EEG and cMRI tests were not performed on this patient. Prescribed medication taken by the patient included an SSRI, mirtazapine, and zopiclone. The retrospective analysis showed that the patient had previously experienced a thoracic skin lesion, precipitating a discussion of cutaneous scleroderma. Raynaud's phenomenon was not present, there was also no evidence of lung or rheumatological involvement. Antinuclear antibodies were negative. Therefore, currently there was no evidence of connective tissue disease in Case 1. However, a developing rheumatological disease cannot be ruled out. Brain involvement of a thoracic cutaneous scleroderma that cannot be definitively excluded is very unlikely according to the literature, but it cannot be excluded safely in the current situation [13]. Case 2 was an approx. 40-year-old male patient with severe chronic depressive disorder. This patient also showed high CSF concentrations of IL-8, IP-10, and IFN-α. The basic CSF diagnostic showed moderate BBB dysfunction with increased total protein (589 mg/l; reference ≤450 mg/l) and increased age-dependent AQs (7.2×10^{-3}; reference 6.5×10^{-3}). This patient underwent both EEG and cMRI, the results of which were inconspicuous. The patient did not receive any medication at the time of lumbar puncture. In summary, both patients with globally abnormal cytokine findings were middle-aged men who suffered from severe depression with prolonged progression. Their basic CSF diagnostics showed signs of slight BBB dysfunction in both cases.

3.6. Correlation analyses

The authors detected a significant correlation between CSF IL-8 concentrations and IP-10 ($r = 0.344$, $p = .030$; $N = 40$). The IL-8 concentrations did not correlate with the psychometric scores. MCP-1 correlated with IFN-α ($r = 0.659$, $p < .001$; $N = 40$) and IP-10 ($r = 0.334$, $p = .035$; $N = 40$). IFN-α correlated with MCP-1 ($r = 0.659$, $p < .001$; $N = 40$), IP-10 ($r = 0.689$, $p < .001$; $N = 40$), CSF protein concentration ($r = 0.466$, $p = .002$; $N = 40$), albumin quotient ($r = 0.347$, $p = .028$; $N = 40$), and number of suicide attempts ($r = 0.449$, $p = .004$; $N = 40$). IP-10 correlated with MCP-1 ($r = 0.334$, $p = .035$; $N = 40$), IFN-α ($r = 0.689$, $p < .001$; $N = 40$), and IL-8 ($r = 0.344$, $p = .030$; $N = 40$).

4. Discussion

The main findings of this study were significantly higher concentrations of IL-8 in the CSF of patients with unipolar depression compared to age-matched mentally healthy controls.

4.1. The present findings in the context of earlier studies

The majority of previous analyses of cytokine concentrations in connection with mental disorders examined cytokine levels in peripheral serum samples. Among the cytokines, high concentrations of IL-6 have in particular been reported. Dowlati and colleagues emphasized the role of IL-6 in their meta-analysis of various cytokines in depressive disorders, but they did not find any difference in IL-8 levels in serum compared to non-depressive patients [8]. However, in the CSF study presented here, IL-8 levels were significantly higher in depressive patients compared to the control group. Maxeiner et al. [25] provided an explanation for this discrepancy. They studied cytokines in the serum and CSF of patients with various neurological and psychiatric diseases and were able to show that cytokine concentrations in CSF differ from those in serum. Among the cytokines measured, IL-8 was the only one for which the concentration in CSF exceeded the serum concentration. The authors concluded that IL-8 is the most sensitive inflammatory marker in CSF [25]. Kern and colleagues investigated IL-8 in the CSF of depressed patients and found highly significant differences in the CSF concentrations of IL-8 compared to those of non-depressed patients [18]. While those results are similar to the results presented here, there are crucial differences between these two studies, especially regarding the age and gender of participants; Kern and colleagues investigated older women exclusively. Other studies investigating CSF cytokine levels also reported high IL-6 levels in the CSF of depressed patients [6,36]. Unfortunately, IL-6 was below the detection limit with the multiplex assay used in the present study. A recent meta-analysis of inflammation markers in the CSF of patients with affective disorders and schizophrenia carried out by Orlovska-Waast and colleagues did not show a significant difference in IL-6 and IL-8 compared to healthy controls [29]. The lack of confirmation of these findings via meta-analytic approaches might be related to the fact that only a small subgroup of patients with unipolar depression suffers from inflammatory processes. Studies examining patients with different underlying pathophysiologies may therefore be negative [46]. Therefore, it can be assumed that IL-8

may play a role in the pathogenesis or maintenance of a subgroup of but not all patients with depressive disorders.

In line with earlier findings [9–12], a high rate of patients with BBB dysfunction was found. AQ levels, which are the reference standard for measuring BBB function, were significantly higher in the patient group compared to the mentally healthy control group. A disturbance of the BBB function might be a sign of a more severe or treatment resistant form of depression.

4.2. Pathophysiological implications of IL-8

IL-8 is an important inflammatory mediator. It is produced in a variety of tissues upon exposure to inflammatory factors, such as tumor necrosis factor (TNF) or IFN. Upon release, it recruits lymphocytes and activates neutrophil granulocytes, which in turn can produce IL-8 themselves, amplifying the inflammatory signal [4,15]. IL-8 is degraded relatively slowly compared to other cytokines and can persist for several days in its active form in the direct environment of the cells from which it has been released [48], which makes it easier to measure in studies than other interleukins. IL-8 can also be produced by a variety of cells inside the CNS, including astrocytes, endothelial cells, and microglial cells, when stimulated by cytokines or other infectious stimuli [1,37,44]. This illustrates the role of IL-8 in the innate and adaptive immune response and shows that up-regulation of IL-8 may be regarded as a pathological condition. A post-mortem study of the brains of depressed patients conducted by Shelton et al. [38] showed increased gene expression of IL-8 in the frontal cortex, further supporting this assumption. CXCR2-receptors for IL-8 can be found on neurons and endothelial cells of the BBB [42], which is especially interesting as TNF-α and IL-6 have previously been connected to disruption of the BBB function. It is possible that IL-8 could have a similar effect. In line with these considerations, the two outlier patients with extremely elevated IL-8 levels in the current study also showed signs of BBB dysfunction. The patient in Case 1 had nonspecific signs with increased protein concentration, and the patient in Case 2 also exhibited increased levels of the more specific AQ. However, there was no correlation between IL-8 and markers for BBB function in the CSF (protein concentration, AQ) over the total group. Microglia also express CXCR2; however, the functional consequences of IL-8 receptor activation in this constellation are still unknown [2]. There is also evidence that IL-8 has neuromodulatory properties. Puma and colleagues were the first to show that IL-8 can directly modulate ion channels, specifically calcium channels, in the brain and reduce calcium currents, thus influencing synaptic activity. This observation indicates that IL-8, through the direct modulation of neuronal excitability, might be an important factor in intercellular communication under normal and pathological conditions [33]. The exact influence of IL-8 on neurotransmitter metabolism has not yet been sufficiently investigated. However, it is likely that, similar to related cytokines in a chronic pro-inflammatory state, elevated levels of IL-8 can lead to disturbance of neurotransmitter systems, possibly through increased reuptake of serotonin (as in the case of IL-1β; [7]). In their recently published review, Stuart and colleagues suggested that IL-8 also affects the hypothalamus-hypophysis axis [43]. This stress axis plays an important role in the development and maintenance of various mental illnesses; and the hyperactivity of the hypothalamus-pituitary gland axis in depressive disorders is a well-known phenomenon [30]. From this perspective, upregulation of IL-8 might be a compensatory response during disease/stress [37]. In summary, IL-8 is a potent pro-inflammatory mediator that promotes the migration of neutrophil granulocytes and other pro-inflammatory cells into inflamed tissues; in addition, it can be secreted by microglia. Furthermore, IL-8 fulfills complex signaling functions. It is quite conceivable that in pathological states, IL-8 can intervene in and modulate various neuronal processes and central metabolic pathways.

4.3. Clinical implications of CSF diagnostics and IL-8 measurements

The IL-8 outlier patients (who also had particularly high levels of IP-10 and IFN-α) were middle-aged male patients who were chronically or recurrently ill with severe depression, with repeated inpatient stays and suicide attempts. The somatic examinations with EEG and cMRI were unremarkable (or not done in Case 1); however, the CSF analyses revealed signs of BBB dysfunction as well as chronic inflammation (i.e., OCBs). This underlines that in patients with similar clinical courses of depression, CSF analysis can provide important indications of inflammatory processes. IL-8 may be a supportive CSF biomarker for this patient subgroup. Especially in Case 2, where nonspecific increased AQ and high total protein concentrations were detected, increased IL-8 levels could support the hypothesis of an inflammatory pathophysiology. In the future, such patients may turn out to be potential candidates for immunomodulatory therapies, although the exact constellations for such therapies clearly require further investigation.

4.4. Limitations

The strengths of this paper are that cytokines were studied in the CSF of a relatively large sample and, additionally, the study included broad neuropsychiatric instrumental findings; however, significant limitations must also be mentioned. First, the assay was not validated for the measurement of CSF. Thus, the IL-6 levels, for example, were below the detectable limit. The transport of the CSF material to the CSF laboratory could also have contributed to the degradation of IL-6. Sensitivity problems in CSF have been previously documented in the literature [23]. Still, studies such as the present study and other studies with CSF material (e.g., [31]) help to validate these useful multiplex assays. Second, lumbar puncture for CSF collection is an invasive procedure, which raises ethical concerns about the recruitment of a healthy control group. Therefore, an idiopathic intracranial hypertension control group without mental illness was created. However, it cannot be ruled out that idiopathic intracranial hypertension may have yet unrecognized links to autoimmunological or inflammatory reactions (cf. [47]), especially because idiopathic intracranial hypertension also seems to be a disease with various causes [39].

The retrospective design of the present study resulted in further relevant limitations. First, the sample processing was not fully standardized. Although all samples underwent the same procedure by being frozen at −80 °C after transport to the CSF laboratory and after basic diagnostics, potential defrosting artifacts for possible diagnostic re-examinations were not documented. Changes in cytokine concentrations could, therefore, be the result of different transport times or defrosting. Second, the intake of potentially influencing psychiatric medication [22] could not be defined as an exclusion criterion for the retrospective patient group. However, the results of the ANOVA test corrected for medication supports the hypothesis that the effect was not primarily driven by medication. Third, the CSF findings could be influenced by psychiatric comorbidities, and information on other potential influencing factors such as nicotine consumption or body mass index were, unfortunately, not available for all patients due to the retrospective design; therefore, their influence should be investigated in future studies. In the retrospectively generated control group, only clinically obtained data were available. To avoid false-positive findings due to already known disorders, patients with neurodegenerative and neurological disorders as well as alcohol or drug abuse were excluded. This means that it is probable that the abnormalities found in this study are related to the core psychiatric pathology. The results apply only to cases of severe depression (all patients in the study had severe depression). As all the patients were not screened with lumbar puncture, but only retrospectively selected, it cannot be excluded that the results are only valid in very severe cases of depression, because lumbar punctures are performed particularly frequently in such cases. Gender matching was not possible. However, the corrected ANOVA model

showed the same significant results. Influencing factors, such as thyroid hormone levels [20], were taken into account but were not shown to play a relevant role. Other influencing factors, such as vitamin D levels [35], should also be considered in future studies.

4.5. Perspectives

Future cross-sectional studies should investigate broader patient samples and cytokine/chemokine profiles to allow subgroup examinations. Longitudinal studies can help to clearly answer the question of whether inflammatory mechanisms in depression are the cause or the consequence of depressive symptoms or the consequence of its pharmacological treatment. Multimodal diagnostics—possibly including CSF examination as part of the basic diagnostic work-up, testing for antineuronal antibodies, IL-6/8 analysis, cMRI, and EEG—could provide a more differentiated causal understanding of depressive syndromes, especially in therapy-resistant patients, thus allowing them to possibly benefit from a therapy tailored specifically to the pathophysiology underlying their symptoms. Patients suffering from therapy-resistant depressive syndromes with immunological causes might benefit from immunomodulatory therapies, whereas patients without immunological signs might, for example, respond better to electroconvulsive therapy if their condition is unresponsive to first-line treatment.

5. Conclusion

Depression is a common and debilitating mental illness. Hypotheses concerning inflammatory and autoimmunological pathogeneses have become increasingly important. In this context, the present study found a significantly higher concentration of IL-8 in the CSF of depressed patients than in a mentally healthy control group. The authors conclude that elevated IL-8 concentrations in CSF might be an additional marker for the detection of inflammatory subgroups of depressive patients. Further research in this field could create the possibility for more targeted approaches to the treatment of depression.

Funding

This work was supported by a grant from the Ministry of Science, Research and the Arts of Baden-Württemberg. The article processing charge was funded by the Baden-Wuerttemberg Ministry of Science, Research and Art and the University of Freiburg in the funding program Open Access Publishing.

Authors' contributions

HK and DE wrote the paper. BLF, LTvE and DE organized the study and created the study design. HK, BLF, NMY, SWS, and FK performed the cytokine measurements. CZ and KD supervised the laboratory work and critically revised the manuscript. RD, BB, and TR performed the CSF basic analyses. NV supported the immunological interpretation, TB and FK supported the neuroanatomical interpretation. SJM and MM supported the statistical analyses. KN, SJM, PS, and KR revised the manuscript critically focusing on clinical and statistical aspects. 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.

Declaration of Competing Interests

HK: None. BLF: None. NMY: None. SWS: None. CZ: None. KN: None. SJM: None. PS: None. KR: None. MM: None. RD: None. BB: Received travel grants and/or training expenses from Bayer Vital GmbH, Ipsen Pharma GmbH, Norvartis, Biogen GmbH and Genzyme, as well as lecture fees from Ipsen Pharma GmbH, Alexion Pharma GmbH, Merck, Sanofi Genzyme and Roche. TR: None. NV: None. FK: None. TB: None. KD: Steering Committee Neurosciences, Janssen. LTvE: Advisory boards, lectures, or travel grants within the last three years: Roche, Eli Lilly, Janssen-Cilag, Novartis, Shire, UCB, GSK, Servier, Janssen and Cyberonics. DE: None.

Acknowledgements

DE was supported by the Berta-Ottenstein-Programme for Advanced Clinician Scientists, Faculty of Medicine, University of Freiburg. PS was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) - 270949263/GRK2162 and PS is supported by the Interdisciplinary Center for Clinical Research (IZKF) Erlangen, clinician scientist programme.

References

[1] Aloisi F, Carè A, Borsellino G, Gallo P, Rosa S, Bassani A, et al. Production of hemolymphopoietic cytokines (IL-6, IL-8, colony-stimulating factors) by normal human astrocytes in response to IL-1 beta and tumor necrosis factor-alpha. J Immunol. 1992;149:2358–66.
[2] Ambrosini E, Aloisi F. Chemokines and glial cells: a complex network in the central nervous system. Neurochem Res. 2004;29:1017–38.
[3] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders5th ed.. ; 2013 DSM-5.
[4] Baggiolini M, Clark-Lewis I. Interleukin-8, a chemotactic and inflammatory cytokine. FEBS Lett. 1992;307:97–101. https://doi.org/10.1016/0014-5793(92)80909-Z.
[5] Berk M, Ng F, Dodd S, Callaly T, Campbell S, Bernardo M, et al. The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. J Eval Clin Pract. 2008;14(6):979–83. https://doi.org/10.1111/j.1365-2753.2007.00921.x.
[6] Carpenter LL, Heninger GR, Malison RT, Tyrka AR, Price LH. Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. J Affect Disord. 2004;79:285–9. https://doi.org/10.1016/S0165-0327(02)00460-3.
[7] 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;9:46–56. https://doi.org/10.1038/nrn2297.
[8] Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67:446–57. https://doi.org/10.1016/j.biopsych.2009.09.033.
[9] Endres D, Dersch R, Hottenrott T, Perlov E, Maier S, van Calker D, et al. Alterations in cerebrospinal fluid in patients with bipolar syndromes. Front Psychiatry. 2016;8:7–194. https://doi.org/10.3389/fpsyt.2016.00194.
[10] Endres D, Perlov E, Dersch R, Baumgartner A, Hottenrott T, Berger B, et al. Evidence of cerebrospinal fluid abnormalities in patients with depressive syndromes. J Affect Disord. 2016;198:178–84. https://doi.org/10.1016/j.jad.2016.03.030.
[11] Endres D, Perlov E, Stich O, Tebartz van Elst L. Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) presenting as major depression. BMC Psychiatry. 2016;16:184. https://doi.org/10.1186/s12888-016-0897-3.
[12] Endres D, Perlov E, Baumgartner A, Hottenrott T, Dersch R, Stich O, et al. Immunological findings in psychotic syndromes: a tertiary care hospital's CSF sample of 180 patients. Front Hum Neurosci. 2015;10(9):476. https://doi.org/10.3389/fnhum.2015.00476.
[13] Ferreli C, Gasparini G, Parodi A, Cozzani E, Rongioletti F, Atzori L. Cutaneous manifestations of scleroderma and scleroderma-like disorders: a comprehensive review. Clin Rev Allergy Immunol. 2017;53(3):306–36. https://doi.org/10.1007/s12016-017-8625-4.
[14] Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJL, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013;10:e1001547. https://doi.org/10.1371/journal.pmed.1001547.
[15] Harada A, Sekido N, Akahoshi T, Wada T, Mukaida N, Matsushima K. Essential involvement of interleukin-8 (IL-8) in acute inflammation. J Leukoc Biol. 1994;56:559–64.
[16] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71:171–86. https://doi.org/10.1097/PSY.0b013e3181907c1b.
[17] Janelidze S, Suchankova P, Ekman A, Erhardt S, Sellgren C, Samuelsson M, et al. Low IL-8 is associated with anxiety in suicidal patients: genetic variation and decreased protein levels. Acta Psychiatr Scand. 2015;131:269–78. https://doi.org/10.1111/acps.12339.
[18] Kern S, Skoog I, Börjesson-Hanson A, Blennow K, Zetterberg H, Ostling S, et al. Higher CSF interleukin-6 and CSF interleukin-8 in current depression in older women results from a population-based sample. Brain Behav Immun. 2014;41:55–8. https://doi.org/10.1016/j.bbi.2014.05.006.
[19] Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health. 2013;34:119–38.
[20] Kobawala TP, Patel GH, Gajjar DR, Patel KN, Thakor PB, Parekh UB, et al. Clinical utility of serum interleukin-8 and interferon-alpha in thyroid diseases. J Thyroid Res. 2011:270149. https://doi.org/10.4061/2011/270149.

[21] Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol Psychiatry Reward Dysfunct Depr. 2009;66:287–92. https://doi.org/10.1016/j.biopsych.2009.01.030.
[22] Liu JJ, Wei YB, Strawbridge R, Bao Y, Chang S, Shi L, et al. Peripheral cytokine levels and response to antidepressant treatment in depression: a systematic review and meta-analysis. Mol Psychiatry. 2019(Aug 19). https://doi.org/10.1038/s41380-019-0474-5.
[23] Malekzadeh A, de Groot V, Beckerman H, van Oosten BW, Blankenstein MA, Teunissen C. Challenges in multi-plex and mono-plex platforms for the discovery of inflammatory profiles in neurodegenerative diseases. Methods Appl Multiplex Technol Biomed. 2012;56:508–13. https://doi.org/10.1016/j.ymeth.2012.03.017.
[24] Martinez JM, Garakani A, Yehuda R, Gorman JM. Proinflammatory and "resiliency" proteins in the Csf of patients with major depression. Depress Anxiety. 2012;29:32–8. https://doi.org/10.1002/da.20876.
[25] Maxeiner H-G, Marion Schneider E, Kurfiss S-T, Brettschneider J, Tumani H, Bechter K. Cerebrospinal fluid and serum cytokine profiling to detect immune control of infectious and inflammatory neurological and psychiatric diseases. Cytokine. 2014;69:62–7. https://doi.org/10.1016/j.cyto.2014.05.008.
[26] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65:732–41. https://doi.org/10.1016/j.biopsych.2008.11.029.
[27] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22–34. https://doi.org/10.1038/nri.2015.5.
[28] Normann C, Frase L, Berger M, Nissen C. Steroid-responsive depression. BMJ Case Rep. 2013;2013. https://doi.org/10.1136/bcr-2013-009101.
[29] Orlovska-Waast S, Köhler-Forsberg O, Brix SW, Nordentoft M, Kondziella D, Krogh J, et al. Cerebrospinal fluid markers of inflammation and infections in schizophrenia and affective disorders: a systematic review and meta-analysis. Mol Psychiatry. 2018;1. https://doi.org/10.1038/s41380-018-0220-4.
[30] Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nat Rev Dis Primers. 2016;2:16065. https://doi.org/10.1038/nrdp.2016.65.
[31] Pardo CA, Farmer CA, Thurm A, Shebl FM, Ilieva J, Kalra S, et al. Serum and cerebrospinal fluid immune mediators in children with autistic disorder: a longitudinal study. Mol Autism. 2017;5:8:1. https://doi.org/10.1186/s13229-016-0115-7 [eCollection 2017].
[32] Pedersen G, Urnes Ø, Hummelen B, Wilberg T, Kvarstein EH. Revised manual for the global assessment of functioning scale. Eur Psychiatry. 2018;51:16–9. https://doi.org/10.1016/j.eurpsy.2017.12.028.
[33] Puma C, Danik M, Quirion R, Ramon F, Williams S. The chemokine interleukin-8 acutely reduces Ca2+ currents in identified cholinergic septal neurons expressing CXCR1 and CXCR2 receptor mRNAs. J Neurochem. 2001;78:960–71. https://doi.org/10.1046/j.1471-4159.2001.00469.x.
[34] Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27:24–31. https://doi.org/10.1016/j.it.2005.11.006.
[35] Ryynänen J, Carlberg C. Primary 1,25-dihydroxyvitamin D3 response of the interleukin 8 gene cluster in human monocyte- and macrophage-like cells. PLoS One. 2013;21(8(10)):e78170. https://doi.org/10.1371/journal.pone.0078170.
[36] Sasayama D, Hattori K, Wakabayashi C, Teraishi T, Hori H, Ota M, et al. Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. J Psychiatr Res. 2013;47:401–6. https://doi.org/10.1016/j.jpsychires.2012.12.001.
[37] Semple BD, Kossmann T, Morganti-Kossmann MC. Role of chemokines in CNS health and pathology: a focus on the CCL2/CCR2 and CXCL8/CXCR2 networks. J Cereb Blood Flow Metab. 2010;30:459–73. https://doi.org/10.1038/jcbfm.2009.240.
[38] Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA, et al. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. Mol Psychiatry. 2011;16:751–62. https://doi.org/10.1038/mp.2010.52.
[39] Sosvorova L, Vcelak J, Mohapl M, Vitku J, Bicikova M, Hampl R. Selected pro- and anti-inflammatory cytokines in cerebrospinal fluid in normal pressure hydrocephalus. Neuro Endocrinol Lett. 2014;35(7):586–93.
[40] Stich O, Rauer S, Kaiser R. Liquordiagnostik. Neurologie Compact - Für Klinik Und Praxis. Baltimore: Thieme; 2013.
[41] Stich O, Andres TA, Gross CM, Gerber SI, Rauer S, Langosch JM. An observational study of inflammation in the central nervous system in patients with bipolar disorder. Bipolar Disord. 2015;17(3):291–302. https://doi.org/10.1111/bdi.12244.
[42] Stuart MJ, Baune BT. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci Biobehav Rev. 2014;42:93–115. https://doi.org/10.1016/j.neubiorev.2014.02.001.
[43] Stuart MJ, Singhal G, Baune BT. Systematic review of the neurobiological relevance of chemokines to psychiatric disorders. Front Cell Neurosci. 2015;9. https://doi.org/10.3389/fncel.2015.00357.
[44] Subileau EA, Rezaie P, Davies HA, Colyer FM, Greenwood J, Male DK, et al. Expression of chemokines and their receptors by human brain endothelium: implications for multiple sclerosis. J Neuropathol Exp Neurol. 2009;68:227–40. https://doi.org/10.1097/NEN.0b013e318197eca7.
[45] Suzuki T, Uchida H, Sakurai H, Ishizuki T, Tsunoda K, Takeuchi H, et al. Relationships between global assessment of functioning and other rating scales in clinical trials for schizophrenia. Psychiatry Res. 2015;227(2–3):265–9. https://doi.org/10.1016/j.psychres.2015.02.024.
[46] Tebartz van Elst L. Vom Anfang und Ende der Schizophrenie - Eine neuropsychiaterische Perspektive auf das Schizophrenie-Konzept. 1st ed.. Stuttgart: Kohlhammer; 2017.
[47] Samancı B, Samancı Y, Tüzün E, Ekizoğlu E, İçöz S, et al. Evidence for potential involvement of pro-inflammatory adipokines in the pathogenesis of idiopathic intracranial hypertension. Cephalalgia. 2017;37(6):525–31. https://doi.org/10.1177/0333102416650705 Epub 2016 May 18.
[48] Remick DG. Interleukin-8. Crit Care Med. 2005;33(12 Suppl):525–31. https://doi.org/10.1097/01.ccm.0000186783.34908.18 S466-7.