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ORIGINAL PAPER

Cerebrospinal fluid biomarker candidates of schizophrenia: where do we stand?

Nenad Vasic · Bernhard J. Connemann · Robert C. Wolf · Hayrettin Tumani · Johannes Brettschneider

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Abstract Here, we review the cerebrospinal fluid (CSF) candidate markers with regard to their clinical relevance as potential surrogates for disease activity, prognosis assessment, and predictors of treatment response. We searched different online databases such as MEDLINE and EMBASE for studies on schizophrenia and CSF. Initial studies on cerebrospinal fluid in patients with schizophrenia revealed increased brain–blood barrier permeability with elevated total protein content, increased CSF-to-serum ratio for albumin, and intrathecal production of immunoglobulins in subgroups of patients. Analyses of metabolites in CSF suggest alterations within glutamatergic neurotransmission as well as monoamine and cannabinoid metabolism. Decreased levels of brain-derived neurotrophic factor and nerve growth factor in CSF of first-episode patients with schizophrenia reported in recent studies point to a dysregulation of neuroprotective and neurodevelopmental processes. Still, these findings must be considered as non-specific. A more profound characterization of the particular psychopathological profiles, the investigation of patients in the prodromal phase or within the first episode of schizophrenia promoting longitudinal investigations, implementation of different approaches of proteomics, and rigorous adherence to standard procedures based on international CSF guidelines are necessary to improve the quality of CSF studies in schizophrenia, paving the way for identification of syndrome-specific biomarker candidates.

Keywords Cerebrospinal fluid · Schizophrenia · Blood-CSF barrier · Cytokines · Proteomics

N. Vasic (✉) · B. J. Connemann
Department of Psychiatry and Psychotherapy III, University of Ulm, Leimgrubenweg 12-14, 89075 Ulm, Germany
e-mail: nenad.vasic@uni-ulm.de

R. C. Wolf
Department of General Psychiatry, Center of Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany

H. Tumani · J. Brettschneider
Department of Neurology, University of Ulm, Ulm, Germany

Introduction

Schizophrenia is the most severe and impairing mental disorder. The life-time-risk amounts to 0.5–1% [51] and worldwide incidence rates of 15 per 100,000 have been reported [85]. Schizophrenia is characterized by disorganization of thought and behavior, along with hallucinations of different modalities, paranoid and delusional beliefs, and mood disturbance, resulting in impairment of core functions of the self. Due to the frequency of severe impairment and the chronic course of the disease, schizophrenia has an enormous impact not only on the health and lifestyle of patients and their relatives but also on the global economic burden of disease [151]. With regard to clinical phenotype, the subtypes of schizophrenia appear markedly heterogeneous, and this might also be true for their etiologies and pathomechanisms. The diagnosis of schizophrenia, however, still fully relies on clinical criteria; there are no sub-type specific and not even disease-specific neuroimaging or biochemical markers. Cerebrospinal fluid (CSF) obviously reflects biochemical changes within the central nervous system (CNS) more directly than does serum [147] and, therefore, CSF might be a useful source of potential biochemical markers of schizophrenia. Several recent studies investigated such biomarker candidates of schizophrenia in CSF [47, 129–131], unhappily without identifying promising one. The

present article reviews the current knowledge on CSF parameters that might be related to aspects of the pathophysiology of schizophrenia.

Basic principles of CSF analysis

CSF is a clear, colorless fluid, which occupies the space between arachnoid mater and pia mater, the subarachnoid space, the ventricles, and the central canal of brain stem and spinal cord. The CSF total volume remains essentially constant at 100–150 ml. However, CSF has a high turnover and is continuously being produced at a rate of about 500 ml per day, predominantly within the choroid plexus, and also continuously being drained, predominantly via arachnoid granulations into the bloodstream. CSF is usually obtained by lumbar puncture, which is generally well tolerated if performed by an experienced clinician using a small-gauge non-traumatic needle [115].The CSF proteins mainly derive from the blood. The Blood-CSF barrier limits the passage of molecules into CSF [108]. Accordingly, the protein concentration in CSF is lower by two to three orders of magnitude compared to serum [133]. The protein content approximates 0.3% of plasma protein content (15–40 mg/dl) while the glucose concentration amounts to 50–70% of plasma glucose concentrations (50–80 mg/dl) [15–17]. Since albumin is produced only in the liver, the ratio of CSF albumin to serum albumin (Qalb) can be used as a measure of Blood-CSF barrier permeability. Standardized age-corrected reference ranges exist for this purpose [112]. Normal CSF contains no cells, although up to 4 leukocytes per microliter are considered non-specific.

CSF basic findings in schizophrenia

With regard to psychiatric disorders, the role of CSF analyses so far is confined to the exclusion of neurological causes [70, 108]. Several studies in patients with schizophrenia reported alterations of basic CSF parameters like total protein content, Qalb, total glucose content, lactate concentration, immunoglobulins, and cellular elements (e.g., [11]).

Total cell count

While the total CSF cell count showed no significant differences between patients with schizophrenia and controls, in several studies by Nikkila and co-workers, acutely psychotic patients were observed to show an increased proportion of activated lymphoid cells as well as elevated proportions of monocytes and macrophages, indicating an activation of microglial cells [98, 99]. With antipsychotic treatment, the number of macrophages was reported to decline.

Glucose and lactate

In drug-naïve patients with first-onset schizophrenia, increased CSF glucose levels and decreased lactate and acetate concentrations were reported, which returned to normal in over half of the patients after short-term treatment with antipsychotic medication [44].

Blood-CSF barrier

Several studies reported increased Blood-CSF barrier permeability in fractions of about 30% of patients with schizophrenia [9, 63]. Axelsson et al. [7] reported increased Qalb in 7 out of 25 patients with schizophrenia as a possible indicator of Blood-CSF barrier impairment; in the subgroup with elevated Qalb, the onset of psychosis occurred 20 years earlier than in patients with normal Qalb, suggesting that Blood-CSF barrier impairment might contribute to the development of psychosis at least in some individuals. Generally, elevation of Qalb is a non-specific finding [20], which could also be attributed to a reduced rate of exchange of CSF [102, 103] and is encountered in a wide range of disorders [20]. In psychiatric diseases, the Blood-CSF barrier dysfunction appears to be more pronounced in schizophrenia than in affective disorders [108]. Still, the mechanisms underlying Blood-CSF barrier dysfunction in a subgroup of patients with schizophrenia remain unclear. Schwarz et al. [132] reported Blood-CSF barrier dysfunction in schizophrenia to be associated with high levels of the soluble intercellular adhesion molecule-1 (sICAM-1), suggesting inflammatory mechanisms. A possible influence of antipsychotic therapy was investigated by Ben-Shachar and colleagues: Administration of haloperidol or chlorpromazine in rats lead to an elevated iron uptake into the brain, indicating a possible affection of Blood-CSF barrier function by neuroleptic treatment [12]. Treatment with antipsychotic or antidepressant drugs might also indirectly contribute to elevated Qalb via an increase in total body weight since increased epidural fat storage and increased central venous pressure [140] both tend to reduce the pressure gradient between CSF and venous compartment, contributing to a reduced CSF exchange rate and an increased CSF protein concentration [20].

Immunoglobulins

Immunoglobulin G synthesis within CSF (oligoclonal bands) indicates an intrathecal immune reaction [128]. Increased immunoglobulin G concentrations within the

CSF can also be caused by an impaired Blood-CSF barrier that may be a consequence of traumatic injury, inflammation, or degenerative spine disease. The IgG-index accounts for CSF–blood barrier permeability by relating the intrathecal IgG production to the CSF/serum albumin ratio (IgG-Index = [IgG(Liquor)/IgG(Serum)]/[Albumin(Liquor)/Albumin(Serum)]; [17]). Increased immunoglobulin G levels in schizophrenia have been described by Toorey and colleagues [145], but this finding could not be reproduced ([1, 19]; Table 1).

Considering the relatively long period in which the majority of studies have been conducted, the different and partly out-dated methodological approaches, as well as the diversity of reported results, basic CSF findings reported in some patients with schizophrenia most likely represent non-specific changes.

Metabolic marker candidates

Glutamatergic metabolites

Decreased levels of gamma-glutamylglutamine and taurine as well as increased levels of isoleucine were found in CSF of 26 drug-free patients with schizophrenia using high-pressure liquid chromatography and gas chromatography/mass spectrometry [31]. A possible hypothesis of dysregulation of glutamatergic neurotransmission would also be

Table 1 Studies of the cerebrospinal fluid in patients with schizophrenia reporting changes in the Blood-CSF barrier permeability and endogenous IgG production in the central nervous system

Study	Blood-CSF barrier permeability	IgG level	Further remarks
Bruetsch et al. [22]	TPC >45 mg/dl in 4,4% of male and 2,7% of female patients	n.r.	634 patients with schizophrenia were studied, one of the first studies at all
Hunter et al. [48]	Increased TPC in 14% of general psychiatric inpatients: >50 mg/dl in females, >60 mg/dl in males	n.r.	256 patients were studied, BCBP changes independent of diagnosis
Hoerster et al. [43]	Elevated TPC	n.r.	Elevated TPC independent of diagnosis
Dencker and Zethraeus [30]	Increased BCBP in male patients compared to female patients	n.r.	2161 patients were studied, BCBP changes independent of diagnosis
Kirch et al. [62]	In 29% of patients increased BCBP	In 33% of patients endogenous CNS IgG production	24 patients with schizophrenia were studied
Kirch et al. [63]	In 22% of patients increased BCBP	In 20% of patients endogenous CNS IgG production	46 patients with schizophrenia were studied, no effect of neuroleptic medication was found
Toorey et al. [145]	n.r.	Elevations of IgG or measles antibody	35% of multiple admission schizophrenic patients had striking IgG elevations
Albrecht et al. [1]	n.r.	Increased CSF/serum antibody ratio for CMV, vaccinia, HSV, and for influenza virus	60 patients with schizophrenia and 26 controls were studied
Bauer and Kornhuber [9]	In 54% of patients increased BCBP	No endogenous CNS IgG production	15 male patients with schizophrenia were studied
Delisi et al. [29]	n.r.	Decreased IgG level in CSF	35 patients with chronic schizophrenia were studied under medication withdrawal
Müller and Ackenheil [90]	TPC >45 mg/dl in 33% and >50 mg/dl in 22% of patients	In 15% of patients elevations of IgG	27 patients with schizophrenia were studied; positive correlation between the rate of CSF albumin and CSF IgG and the subscores for the negative symptoms
Axelsson et al. [7]	In 28% of patients increased BCBP	n.r.	25 patients with schizophrenia were studied; onset of psychosis had occurred, on average, 20 years earlier in the patients with impairment of the Blood-CSF barrier than in those without
Schwarz et al. [132]	In 17,5% of patients increased BCBP	n.r.	An increased BCBP was associated with high levels of the soluble intercellular adhesion molecule-1 (sICAM-1)
Torrey et al. [146]	In 7% of patients increased BCBP and elevated TPC	n.r.	In this study most patients with schizophrenia had intact BCBP

TPC total protein content, *BCBP* Blood-CSF barrier permeability, *CSF* cerebrospinal fluid, *CNS* central nervous system, *n.r.* not reported

supported by studies analyzing D-serine. D-serine is an endogenous agonist of the glycine site on the N-methyl-D-aspartate (NMDA) glutamate receptor (see Fig. 1). Decreased levels of D-serine and reduced D-serine-to-totaL-serine ratio but elevated levels of total and L-serine were found in serum of 42 patients with schizophrenia [40]. At the same time, D-serine level and D-/L-serine ratio in plasma have been shown to increase with clinical improvement [100]. Reduced D-serine-to-total-serine ratio was also found in CSF of male, first-episode, drug-naïve patients with schizophrenia [39], possibly due to increased levels of D-amino acid oxidase (DAAO; it degrades D-serine) and decreased serine racemase levels (converts L-serine to D-serine), which have been demonstrated in a post-mortem study of brain tissue [13]. However, the expression of DAAO and serine racemase as well as corresponding mRNA levels seem to vary considerably depending on the brain region investigated [153] and administration of haloperidol did not affect serine racemase or DAAO levels in rats [153]. One study reported unaltered levels and relative ratios of D-serine in CSF before and after 6 weeks of treatment with olanzapine 10 mg/die [37]; Table 2.

Fatty acids

Polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are linked with several aspects of neural function, including neurotransmission, membrane fluidity, ion-channel and enzyme regulation, and gene expression [159]. Decreased blood levels of omega-3 fatty acids have been associated with a number of neuropsychiatric disorders including

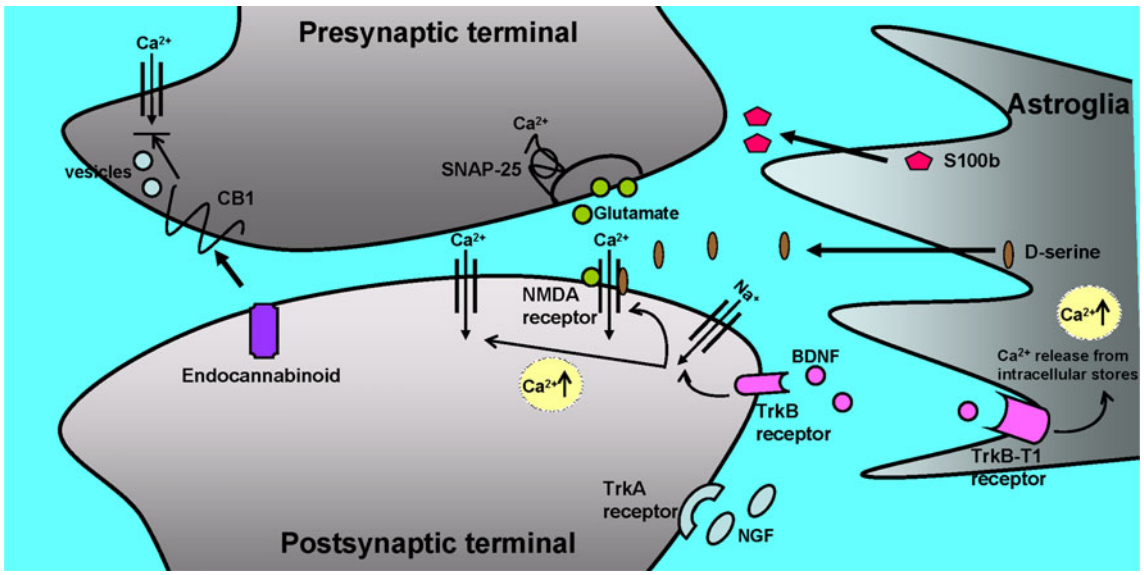

Fig. 1 Molecular mechanisms being involved in the pathogenesis of schizophrenia, as indicated by the CSF findings. *Endocannabinoids* leave the post-synaptic cell and activate presynaptic CB1 receptors, which than inhibit Ca^{2+} influx and thereby decrease the probability of release of neurotransmitter vesicles [155]. Thus, the reported increased CSF anandamide in schizophrenia may contribute to the reduction of—in some regions possibly abnormal increased—neurotransmitter secretion, and therefore, might represent a protective factor, which was found to be negatively correlated with severity of psychosis [38]. *D-serine* binds to the glycine/D-serine-binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor. In conjunction with the binding of glutamate, this leads to opening of the ligand-gated Ca^{2+}-receptor-channel [93]. Decreased levels of D-serine in schizophrenia might support the notion of the altered—presumably reduced—functioning of the NMDA receptor, which is modulated by both glutamate from the synaptic cleft and the D-serine stemming from astrocytes. As a part of the Trans-SNARE complexes (together with synaptobrevin and syntaxin), *SNAP-25* is involved in the Ca^{2+}-triggered exocytosis of neurotransmitters [25]. The reported increased CSF levels of SNAP-25 in schizophrenia would support the notion of the dysfunctional synaptic secretion of neurotransmitters. The binding of the brain-derived neurotrophic factor (*BDNF*) to the post-synaptic TrkB receptors causes depolarization of the post-synaptic neuron. This process is mediated through opening of Na^{+} channels and concomitant activation of Ca^{2+} channels [80]. The activation of TrkB receptors enhances also NMDA receptor opening, resulting in an overall increase of the intracellular Ca^{2+} concentration. In astroglia, the BDNF binding to the TrkB-T1 receptors activates the release of Ca^{2+} from the intracellular stores, thereby increasing intracellular Ca^{2+} concentration [113, 116]. By its binding to the TrkA receptors, the nerve growth factor (*NGF*) initiates an intracellular signal cascade [160], thereby enhancing and coordinating the neurogenesis and neural survival. Decreased CSF levels of both BDNF and NGF indicate alterations in the process of neurogenesis in schizophrenia. Increased levels of *S100b* can be attributed to the increased activation of astrocytes, possibly as a sign of a genuine glia cells dysfunction or their response within an inflammatory reaction. Glial fibrillary acidic protein (*GFAP*) was not found to be altered in schizophrenia, suggesting that the increase in S100B might indeed be caused by an active secretion of S100b from astrocytes rather than by a destruction of astrocytes, oligodendrocytes or neurons [119]. Furthermore, no alterations in the levels of *tau protein* and neuron-specific enolase (*NSE*) could be found, indicating that no major neuro-axonal damage occurs

Table 2 Studies of metabolic biomarkers in cerebrospinal fluid of patients with schizophrenia

Study	Biomarker, description/function	Sample description	Main findings in CSF
Metabolic markers			
Hashimoto et al. [39]	D-serine: endogenous agonist of the glycine site on the N-methyl-D-aspartate (NMDA) glutamate receptors	25 male first-episode medication-naïve patients with schizophrenia	Reduced D-serine-to-total serine ratio
Do et al. [31]	Gamma-glutamylglutamine: reflects a system involved in glutamate uptake, or a deficiency in glutamine, an important precursor of releasable glutamate	26 medication-free patients with schizophrenia	Decreased levels of gamma-glutamylglutamine and taurine as well as increased levels of isoleucine
Fuchs et al. [37]	D-serine: endogenous agonist of the glycine site on the N-methyl-D-aspartate (NMDA) glutamate receptors	19 patients with schizophrenia	Unaltered levels and relative ratios of D-serine before as well as after 6 weeks of treatment with olanzapine 10 mg/die
Holmes et al. [44]	Glucose, lactate, acetate: metabolic products reflecting gluco-, lipid-, and mitochondrial functioning	152 medication-naïve or minimally treated patients with first-onset schizophrenia	Increased CSF glucose level and decreased lactate and acetate concentrations, which normalized in over half the patients after short-term treatment with antipsychotic medication
Miller et al. [86]	Dopamine, dihydroxyphenylacetic acid (DOPAC), noradrenaline, 5-hydroxytryptamine (5-HT), 5-hydroxyindolacetic acid (5-HIAA), chromogranin A, and secretogranin II: biogenic amines, their metabolites, and constituents of large dense-core vesicles	First-episode medication-naïve patients with schizophrenia	No significant difference between controls and schizophrenic patients
Kahn et al. [59]	Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA): metabolites of dopamine and serotonin	16 schizophrenic and 3 schizoaffective male inpatients	Neuroleptic treatment with haloperidol 20 mg/die significantly increased HVA concentrations and significantly increased the ratio between HVA and 5-HIAA
Scheepers et al. [118]	Homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA): metabolites of dopamine and serotonin	23 male patients with schizophrenia, medication-free for at least 2 weeks	Neuroleptic treatment with olanzapine 10 mg/die significantly raised HVA concentrations and significantly raised the ratio between HVA and 5-HIAA
Jacobsen et al. [52]	Homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG): monoamine metabolites	18 patients with onset of schizophrenia by age of 12	CSF monoamine concentrations and ratios of HVA/5-HIAA and HVA/MHPG did not significantly change after 6 weeks of either haloperidol (ca. 20 mg/die) or clozapine (ca. 230 mg/die) treatment
Koethe et al. [64]	Anandamide: endogenous cannabinoid, bioactive lipid binding to cannabinoid receptors	27 patients with schizophrenia in the prodromal state	Anandamide was significantly elevated in patient group, and patients with lower levels showed a higher risk for transiting to psychosis
Giuffrida et al. [38]	Anandamide: endogenous cannabinoid, bioactive lipid binding to cannabinoid receptors	47 first-episode medication-naïve patients with schizophrenia	Higher anandamide levels in patients with schizophrenia compared to healthy controls, patients with dementia or affective disorders; anandamide was negatively correlated with psychotic symptoms
Leweke et al. [75]	Anandamide, palmitylethanolamide, 2-arachidonylglycerol: endocannabinoid lipids	10 patients with schizophrenia	Anandamide and palmitylethanolamide were elevated in patient group, 2-arachidonylglycerolm not
Leweke et al. [74]	Anandamide: endogenous cannabinoid, bioactive lipid binding to cannabinoid receptors	47 first-episode medication-naïve patients with schizophrenia	Decreased anandamide in high-frequency cannabis consumers within schizophrenic patients compared to both high-frequency healthy subjects and less frequently consuming patients
Kozlovsky et al. [69]	Glycogen synthase kinase (GSK)-3ß: serine/thyreonine protein kinase involved in signal transduction affecting neurogenesis and apoptotic processes	6 patients with schizophrenia, 17 healthy control subjects	Reduction of GSK-3ß in patients group

Reported are the examined metabolite, characteristics of the patients group that was studied and the essential findings

schizophrenia, and some supplementation studies suggest benefits in terms of decreasing disease risk and reducing symptoms, particularly in patients with a short illness history [4]. Still, results remain inconclusive [58] and no investigations of PUFAs or their metabolites in CSF have been conducted.

Monoamine metabolites

The concentrations of dopamine, dihydroxyphenylacetic acid (DOPAC), norepinephrine, 5-hydroxytryptamine (5-HT), and 5-hydroxyindolacetic acid (5-HIAA) did not differ in first-onset drug-naive schizophrenia patients when compared to controls [86]. Treatment with haloperidol, 20 mg/die [59], or olanzapine, 10 mg/die [124], was reported to elevate the homovanillic acid (HVA) concentration in the CSF and significantly increase the ratio between HVA and 5-HIAA, a serotonin metabolite, in adult patients with schizophrenia although a correlation with clinical effectiveness could not be definitely established. In contrast, a similar regime (haloperidol and clozapine) did not significantly change CSF monoamine concentrations or the ratio between HVA and 5-HIAA in a group of drug-free patients with childhood-onset schizophrenia [52]. Furthermore, treatment with clozapine had similar effects both in childhood-onset and later-onset schizophrenia.

Cannabinoid metabolites

The endogenous cannabinoid anandamide is a bioactive lipid that binds to cannabinoid receptors. Anandamide concentrations were shown to be increased both in prodromal states [64] and during acute episodes [38, 75] of schizophrenia; Table 2. CSF anandamide appeared to be negatively correlated with severity of psychosis [38], suggesting that anandamide elevation might reflect a compensatory adaptation to the disease state. Patients with schizophrenia who consumed cannabis had lower CSF concentrations of anandamide when compared to both more frequently consuming healthy subjects, or less frequently consuming schizophrenic patients, indicating that intensive cannabis abuse might down-regulate anandamide signaling in patients with schizophrenia and therefore increase the risk of disease manifestation [74]. The neuroimaging data suggest that first-episode schizophrenia patients who use cannabis show a more pronounced cortical thinning than non-using patients, particularly in brain regions known for their high density of CB1 receptors (see Fig. 1), such as the anterior cingulate cortex and the dorsolateral prefrontal cortex [109]. Thus, it seems advisable to discriminate between the endogenous cannabinoid system, which indeed seems to be altered in schizophrenia (as indicated by increased CSF anandamide or increased density of CB1 receptor binding in some brain areas; though possibly having also protective role to some extent, see above), and the exogenous cannabis consumption, which is a risk factor enhancing the manifestation and progression of disorders from the schizophrenia spectrum, possibly by negatively affecting the endogenous cannabinoid system [36].

Glycogen synthase kinase 3 (GSK-3)

Whereas GSK-3 proteins were originally identified as key regulatory enzymes in glucose metabolism, nowadays it is well-known that GSK-3s (two isoforms, GSK-3alpha and GSK-3beta) mediate various signaling pathways, in particular the growth factor and Wnt signaling pathways. GSK-3s has a number of transcription factors as substrates, thereby being involved in regulation of multiple neurodevelopmental processes including neurogenesis, neuronal migration, neuronal polarization, and axon growth and guidance [49]. The investigation of GSK-3alpha and GSK-3beta mRNA levels, GSK-3beta protein levels, or total GSK-3 (alpha + beta) enzyme activity in lymphocytes of patients with schizophrenia revealed no differences compared to controls [95]. Therefore, determination of GSK-3 in CSF could provide additional information regarding the pathogenetic role and possible therapeutic consequences in schizophrenia [65]. Both GSK-3beta levels [67] and GSK-3 activity [66] were reported to be lowered in post-mortem frontal cortex of patients with schizophrenia, possibly suggesting that low GSK-3 in post-mortem brain of schizophrenic patients might be a late consequence of perinatal neurodevelopmental insult in schizophrenia [68]. Still, post-mortem studies do not consistently show GSK-3 alterations in patients with schizophrenia [94]. Only one study investigated GSK-3beta in CSF in alive patients with schizophrenia, using Western-blot analysis and showing decreased levels ([69]; Table 2). However, only 6 patients were studied, the patients had a long duration of illness, in average over 30 years, and the difference in GSK-3beta protein levels was only marginally significant ($P = 0.048$), so that further studies are necessary.

Inflammatory marker candidates

Interleukins

Several studies observed neuroimmunological abnormalities in patients with schizophrenia, including alterations of various cytokines with a wide range of immunomodulatory, neurodevelopmental, and neuroregulatory functions [71]. Particularly, proinflammatory cytokines seem to be altered in some cases of schizophrenia ([71]; Table 3).

Increased CSF levels of both interleukin-6 (IL-6) [150] and interleukin-2 (IL-2) [84] have been reported. In one study [84], patients with a later relapse, examined both while treated (haloperidol) and after drug withdrawal (up to 6 weeks), had higher levels of CSF IL-2 than patients who did not relapse. Therefore, increased CSF IL-2 levels were proposed to predict disease progress. No similar association could be found for blood levels, suggesting independent regulation of blood and CSF cytokine levels. Elevated levels of CSF IL-2, but not interleukin-1 alpha (IL-1α), were also found in antipsychotic-free patients with schizophrenia [77]. Other studies reported no alteration of CSF IL-1, IL-2, or IL-6 levels [8, 34, 61, 110].

Antiphospholipid antibodies

One study demonstrated different patterns of antiphospholipid antibodies in CSF of patients with schizophrenia compared to serum indicating possible intrathecal synthesis [136].

Table 3 Studies of inflammatory markers and infectious agents in cerebrospinal fluid of patients with schizophrenia

Study	Biomarker, description/function	Sample description	Main findings in CSF
Inflammatory markers			
Van Kammen et al. [150]	Interleukin 6 (IL-6): cytokine, regulation factor within inflammatory cascade	61 medication-free male patients with schizophrenia	Not significant elevation of IL-6 in patient group
McAllister et al. [84]	Interleukin 2 (IL-2): cytokine, neuroregulatory function	79 male patients with schizophrenia	Relapse-prone patients had significantly higher levels of interleukin-2 than patients who did not relapse after haloperidol withdrawal for up to 6 weeks
Licinio et al. [77]	Interleukin 1 alpha (IL-1 alpha), interleukin 2 (IL-2): cytokine, neurodevelopmental and neuroimmune processes	10 medication-free patients with schizophrenia	Increased IL-2, but not IL-1 alpha in patient group
Katila et al. [61]	Interleukin 1 (IL-1), interleukin 6 (IL-6): cytokine, neurodevelopmental and neuroimmune processes	14 patients with schizophrenia	No group differences
Rapaport et al. [110]	Interleukin 1 alpha (IL-1 alpha), interleukin 2 (IL-2): cytokine, neurodevelopmental and neuroimmune processes	60 patients with schizophrenia	No group differences
Barak et al. [8]	Interleukin 1 beta (IL-1 beta), interleukin 2 (IL-2), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF alpha): neurodevelopmental and neuroimmune processes	16 patients with schizophrenia	IL-2, IL- 6, TNF alpha showed no group differences; IL-1 beta decreased in patient group
El-Mallakh et al. [34]	Interleukin 1 alpha (IL-1 alpha), interleukin 2 (IL-2): cytokine, neurodevelopmental and neuroimmune processes	Medicated and medication-free patients with schizophrenia	No group differences
Sokol et al. [136]	Antiphospholipid antibodies (aPL): antibodies against cell membrane elements such as cardiolipin and ß$_2$ glycoprotein I	100 psychotic patients having hallucinations and/or delusions	In a subgroup of patients different patterns of aPLs compared to that one in serum
Infectious agents			
Leweke et al. [40]	Toxoplasma gondii, cytomegalovirus, human herpesvirus type 6, herpes simplex virus type 1, herpes simplex virus type 2, Epstein Barr virus	36 medication-naive first-episode patients with schizophrenia; 10 medication-free patients who had received antipsychotic treatment in the past, 39 inpatients under medication	Increased levels of IgG antibodies to both cytomegalovirus and toxoplasma gondii in untreated patients, lower levels in patients under neuroleptic treatment

Reported are the examined biomarker, characteristics of the patients group that was studied and the essential findings

Infectious agents

Cytomegalovirus, toxoplasma gondii, HSV 1, HSV 2, Epstein Barr virus

Various infectious agents have been discussed as candidate pathogenic agents in schizophrenia, including toxoplasma gondii, cytomegalovirus [3, 96, 158], as well as herpes simplex virus (HSV) type 1, 2, and 6 [97, 157]. Elevated levels of serum immunoglobulin G antibodies against these microbial agents were observed both in individuals at high risk for psychosis and in patients with schizophrenia and were suggested to be linked to the severity of psychotic symptoms. Leweke and colleagues reported increased levels of CSF IgG antibodies to both cytomegalovirus and toxoplasma gondii in untreated individuals with recent-onset schizophrenia whereas levels of immunoglobulin M antibodies were not altered [73]; Table 3). There was no difference in the levels of antibodies against HSV 1, HSV 2, and Epstein Barr virus. Interestingly, patients who received neuroleptic treatment had lower levels of antibodies to cytomegalovirus and toxoplasma gondii, suggesting that treatment with neuroleptics could influence B-cell immunology associated with immunoglobulin synthesis in the CNS. So far, conclusive data are missing, and the link between immunology and schizophrenia remains to be elucidated.

Neurotrophic factors

The neurotrophins (nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3, neurotrophin 4, and neurotrophin 5) are proteins with high affinity to receptors of the tyrosine kinase family (TrkA, B, C). By regulating synaptic activity and neurotransmitter synthesis (see Fig. 1), they stimulate and control cellular proliferation, migration, differentiation, and the survival of the neurons not only during the embryo- and organogenesis, but also during the nerve regeneration, enabling, and supporting neural plasticity [32]. Alterations in the expression of the neurotrophins were suggested to contribute to the pathology of schizophrenia, indicating the deficiency of endogenous neuroprotective mechanisms.

Brain-derived neurotrophic factor (BDNF)

Decreased serum BDNF has repeatedly been observed in drug-naïve first-episode schizophrenic patients [23, 26, 114]. Jindal and colleagues showed that patients with schizophrenia had lower serum BDNF levels than patients with non-schizophrenia psychosis that had lower BDNF levels than healthy controls [57]. In a post-mortem brain tissue of patients with schizophrenia, increased BDNF levels and decreased levels of neurotrophin 3 in cortical areas as well as decreased levels of BDNF in hippocampus were found [32]. In another post-mortem study, decreased BDNF levels in prefrontal cortex and in the CSF were found. Also, a significant negative correlation between BDNF and cortisol was observed both in prefrontal cortex tissue and in CSF. Within the same study, these findings could be replicated in an animal model of schizophrenia [50]; Table 4. In one study, serum and CSF BDNF levels were correlated with each other, both showing a negative correlation with the scores of baseline PANSS positive symptom subscalesclinical scores of positive symptoms [106].

Nerve growth factor (NGF)

Kale et al. [60] reported decreased levels of NGF in both CSF and serum in drug-naïve first-episode patients with schizophrenia; Table 4). CSF studies on further neurotrophic factors such as neurotrophin-3, neurotrophin-4, and novel neurotrophin-1 are lacking.

Neuronal marker candidates

Patients with schizophrenia exhibit minor abnormalities on cerebral imaging including enlarged third or lateral ventricles or reduced volume of temporal lobe structures [107], which could be related to causes or consequences of the disease. The current longitudinal investigations suggest that particularly frontal and temporal cortical areas show progressive thinning across the course of the illness [149], although these changes might rather be attributed to the reduction of the neuropil, and not mainly to the degeneration of the neurons (see below the chapter about the glial marker candidates). Also different expression levels of myelin basic protein and myelin oligodendrocyte protein in patients with schizophrenia were found in both CSF and post-mortem mediodorsal thalamus, suggesting alterations within oligodendrocyte and cytoskeleton assembly [82].To elucidate the role of neurodegeneration, several studies investigated particularly various CSF markers of neuronal damage in schizophrenia.

Tau protein

Tau protein is a microtubule-associated phospho-protein that is primarily localized in axons promoting microtubule assembly and stability. After neuronal damage, tau is released into extracellular space from where it diffuses into the CSF [152]. Elevation of CSF tau has been reported in a wide range of neurodegenerative diseases, with highest

Table 4 Studies of neurotrophic, neuronal (damage), and glial biomarkers in cerebrospinal fluid of patients with schizophrenia

Study	Biomarker, description/function	Sample description	Main findings in CSF
Neurotrophic factors			
Pillai et al. [106]	Brain-derived neurotrophic factor (BDNF): neuroprotective and neurodevelopmental factor	34 medication-naïve first-episode patients with schizophrenia and 36 controls, examination of both serum and CSF	Decreased level of BDNF in patient group, which negatively correlated with psychotic symptoms
Issa et al. [50]	Brain-derived neurotrophic factor (BDNF), cortisol	Post-mortem study of patients with schizophrenia	BDNF levels were decreased in prefrontal cortex and CSF in patients group, negatively correlating with cortisol levels
Kale et al. [60]	Nerve growth factor (NGF): neurotrophic factor involved in neurogenesis	30 medication-naïve first-episode patients with schizophrenia and 42 controls, examination of both serum and CSF	Decreased levels of NGF in both CSF and serum
Neuronal (damage) markers			
Schöenknecht et al. [126]	Tau protein, phosphor-tau: a phosphorylated microtubule-associated protein localized in neuronal axons promoting microtubule assembly and stability	10 young (age range: 21–38 years) and 9 patients of older age (age range: 54–70 years) with schizophrenia who were all treated with neuroleptics as compared to normal controls	No significant differences in CSF total tau and phosphor-tau levels were observed between patients with schizophrenia and controls
Steiner et al. [139]	Neuron-specific enolase (NSE): converts 2-phospho-glycerate to phosphoenolpyruvate and is elevated in conditions of neuronal injury	12 patients with first-onset schizophrenia and 17 controls	No significant difference of CSF NSE between patients and controls was detected
Egan et al. [33]	Neuron-specific enolase (NSE): it is elevated in conditions of neuronal injury	50 patients with schizophrenia (recent onset as well as chronic) and 23 normal controls	No significant difference of CSF NSE between patients and controls was detected
Schroeter et al. [127]	Neuron-specific enolase (NSE): it is elevated in conditions of neuronal injury	20 patients with schizophrenia and 19 controls	No significant difference of CSF NSE between patients and controls was detected
Li et al. [76]	Neuron-specific enolase (NSE): it is elevated in conditions of neuronal injury	33 patients with first-episode schizophrenia and 9 controls	NSE was significantly elevated in schizophrenia as compared to controls
Martins-de-Souza et al. [81]	Myelin basic protein, myelin oligodendrocyte protein	17 patients with first-onset schizophrenia, 10 healthy control subjects	Altered expression of myelin basic protein and myelin oligodendrocyte protein in patients with schizophrenia both in CSF and in post-mortem mediodorsal thalamus
Glial markers			
Rothermundt et al. [120]	S100b: calcium-binding protein, affecting the brain cell energy metabolism and the integrity of the cytoskeleton	21 untreated patients with schizophrenia and 21 normal controls	CSF S100b was significantly elevated in patients with schizophrenia
Steiner et al. [139]	S100b: calcium-binding protein, affecting the brain cell energy metabolism and the integrity of the cytoskeleton	12 patients with first-onset schizophrenia and 17 controls	CSF S100b was significantly elevated in patients with schizophrenia

Reported are the examined biomarker, characteristics of the patients group that was studied and the essential findings

levels observed in diseases with a rapid neuro-axonal degeneration like Creutzfeldt-Jakob disease (CJD) [101]. In patients with schizophrenia, CSF tau levels are usually normal [126], providing evidence against major neuro-axonal degeneration in schizophrenia; Table 4. On a clinical level, normal CSF tau in elderly patients with cognitive deficits and possible schizophrenia may help to delineate Alzheimer's disease (AD), which is often accompanied by an early elevation of CSF tau protein [18].

Neuron-specific enolase (NSE)

Enolase is a glycolytic enzyme, consisting of three subunits (α, β and γ), which converts 2-phospho-glycerate to

phosphoenolpyruvate [21]. In the CNS, the $\alpha\gamma$ and $\gamma\gamma$ isoforms are mainly localized within neurons and are therefore called neuron-specific enolase (NSE). Like tau protein, NSE was observed to be elevated in conditions of neuronal injury [156] with highest CSF levels observed in conditions of rapid neuro-axonal degeneration [10]. In line with observations on tau protein, several studies reported normal CSF NSE in schizophrenia [33, 127, 139]; Table 4. Elevated NSE levels were reported by a Chinese study, which however, included a disproportionate low number of controls ($n = 9$) [76]. The present CSF findings regarding tau protein and NSE do not support the notion of major neuro-axonal damage in schizophrenia, although a slow-going, persistent degenerative process, concerning both neuropil and neural tissue, as suggested by neuroimaging findings, cannot be ruled out.

Glial marker candidates

S100b

S100B, a calcium-binding astrocyte-specific cytokine, presents a marker of astrocytic activation [119], Fig. 1. It is an acidic calcium-binding protein with a molecular weight of 21 kD [161]. S100b exerts various autocrine and paracrine effects on glia, neurons, and microglia. It was suggested to play a role in the regulation of cerebral energy metabolism as it stimulates the enzymatic activity of fructose-1,6-bisphosphate aldolase [162]. S100b influences the integrity of the cytoskeleton by inhibiting the assembly of microtubules and type III intermediary filaments [14]. Whereas in nanomolar levels, it acts as a neurotrophic factor and was suggested to promote neuronal survival in brain development and following neuronal injury, overproduction to micromolar levels was shown to exacerbate neuroinflammation and neuronal dysfunction [148]. Increased serum or CSF concentrations of S100b have been reported in a wide range of neurological diseases associated with neuronal damage and glial activation, including cerebral ischemia, subarachnoid hemorrhage, multiple sclerosis, AD, or traumatic brain injury [24, 35, 53, 89]. In patients with schizophrenia, several studies consistently observed S100b to be elevated in CSF ([122, 139]; Table 4) or blood [72, 78, 121, 123, 125, 154]. So far, it is unclear whether increased levels of S100B in CSF and serum play a specific pathophysiological role in schizophrenia. An association of schizophrenia with certain S100B haplotypes has been observed, which may lead to a tendency for increased S100B expression [79]. Findings from neuropathological and imaging studies reveal a reduction of neuropil in schizophrenia that may have a progressive component [135]. Neuronal cell sizes as well as dendrite and synapse numbers are decreased while the total number of neurons appears to remain unchanged [134]. Astrocytes influence dendrites and synapses via glutamate-induced modulation [5]. A dysfunction of astrocytes could be linked to the above-mentioned alterations of neuropil and might therefore represent an independent pathogenetic factor in the development of schizophrenia [120]. On the other hand, increased astrocyte activation, as indicated by increased CSF S100b concentrations, might be an unsuccessful attempt of the brain to fight an unknown pathogenic mechanism, such as inflammation of unidentified origin (as suggested by Rothermundt and colleagues, [119]). So far, no correlation of CSF S100b with clinical parameters like duration of disease or clinical scores was observed [120, 139].

Glial fibrillary acidic protein (GFAP)

GFAP is the major structural component of the intermediate filament of fibrillary astrocytes [54]. High CSF levels of GFAP were observed in conditions of acute CNS injury with disintegration of astroglial cells [6, 41]. Chronic brain disorders with (reactive) gliosis such as AD, vascular dementia, or multiple sclerosis also entailed an increase of GFAP levels [28, 88]. Consequently, GFAP has been proposed to be both a marker of CNS tissue disintegration and astrogliosis [28, 105, 117]. In a study of patients with schizophrenia, Steiner et al. [139] observed CSF S100b to be elevated, whereas no significant alteration of GFAP was found, indicating that GFAP may be less sensitive than S100b to detect an alteration of astrocyte function in schizophrenia.

Proteomic analyses in the identification of possible CSF biomarkers

VGF23-62, transthyretin, apolipoprotein A-IV

Jiang and colleagues studied the CSF proteome in patients with schizophrenia by two-dimensional gel electrophoresis and matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). They report altered levels of CSF apolipoprotein A-IV in patients with schizophrenia, as well as altered levels of haptoglobin, fibrinogen, and complement component 3 [56]. Using similar methodology, the upregulation of apolipoprotein E, apolipoprotein A1, and prostaglandin-H2 D-isomerase has been reported, supporting the hypothesis of disturbed cholesterol and phospholipid metabolism in schizophrenia [83]. Using surface-enhanced laser desorption/ionization (SELDI), Huang and colleagues observed an increase of the 40-amino acid VGF23–62 peptide and a decrease of

Table 5 Proteome studies of cerebrospinal fluid of patients with schizophrenia

Study	Biomarker, description/function	Sample description	Main findings in CSF
Proteome studies			
Jiang et al. [56]	Apolipoprotein A-IV: involved in cholesterol and phospholipid metabolism	10 patients with schizophrenia, 10 healthy control subjects	Decreased level of apolipoprotein A-IV was significantly decreased in patients with schizophrenia
Huang et al. [45]	VGF23–62 peptide: VGF is involved in the control of food intake, body weight, reproduction, neurogenesis, synaptic plasticity Transthyretin: transport of thyroxine	58 medication-naïve patients with first-onset schizophrenia or brief psychotic disorder due to duration of illness	Increase of VGF23-62, decrease of transthyretin, confirmed also in post-mortem brain investigation of a separate patient sample
Huang et al. [46]	VGF23–62 peptide: VGF is involved in the control of food intake, body weight, reproduction, neurogenesis, synaptic plasticity Transthyretin: transport of thyroxine	24 patients with initial prodromal symptoms	Increased levels of glucose and VGF23-62 peptide and decreased levels of lactate and transthyretin in the subjects with initial prodromal symptoms
Thompson et al. [144]	Synaptosome-associated protein of 25 kDa (SNAP-25): regulates presynaptic vesicle trafficking and synaptic secretion	8 acutely psychotic patients with schizophrenia, compared with control subjects, headache patients and bipolar manic patients	Elevated SNAP-25 in patients with schizophrenia, but no significant difference between bipolar patients and patients with schizophrenia
Thompson et al. [143]	Synaptosome-associated protein of 25 kDa (SNAP-25): regulates presynaptic vesicle trafficking and synaptic secretion	25 haloperidol-treated patients with chronic schizophrenia, subdivided in verum and placebo group	Elevated SNAP-25 in patients with schizophrenia independent of treatment
Martins-de-Souza et al. [81]	Apolipoprotein E, A1: involved in cholesterol and phospholipid metabolism	17 patients with first-onset schizophrenia, 10 healthy control subjects	Increase of apolipoprotein E, apolipoprotein A1 and prostaglandin-H2 D-isomerase

Reported are the examined biomarker, characteristics of the patients group that was studied and the essential findings

transthyretin in CSF of first-onset, drug-naïve patients with schizophrenia. Corresponding results were found post-mortem in brain samples [45]; Table 5). No differences regarding the schizophrenia biomarker panel were found when compared with patients with obsessive-compulsive disorder or Alzheimer's disease. Although the function of the VGF23–62 sequence is still unknown, there is data to suggest that the full-length neuroprotein VGF is involved in the control of food intake, body weight and reproduction [55], and also in mediating antidepressant responses. The transcription of VGF is regulated by both brain-derived neurotrophic factor (BDNF) and serotonin. VGF can be upregulated also by antidepressant drugs and voluntary exercise and is reduced in animal models of depression [142]. Furthermore, VGF enhances hippocampal synaptic plasticity as well as neurogenesis in the dentate gyrus [2]. Regarding CSF transthyretin, over 90% is secreted from the choroid plexus, and the rest derives from blood [111]. Since transthyretin is responsible for thyroxine transport [137], decreased transthyretin concentrations may reduce the transport of thyroxine in the brain, possibly abetting the development of psychotic symptoms. A proteomic and metabolic profile with increased glucose and VGF23-62 peptide and decreased lactate and transthyretin, similar to the one described above for first-onset schizophrenia, was also reported for patients in the initial prodromal state of psychosis, suggesting more or less continuous alterations in the CSF metabolome and proteome along a gradient "healthy state—prodromal symptoms of the psychosis—first manifestation of the schizophrenia" [46]; Table 5. In this study, the presence of biochemical alterations in the individuals with prodromal symptoms did not correlate with the risk of developing schizophrenia. Still, this method can be applied to isolate molecular biomarkers in CSF that might support diagnosis at an early stage and characterize mechanisms of disease progression by tracking alterations of parameters along the course of the disease.

Synaptosome-associated protein of 25 kDa (SNAP-25)

SNAP-25 is expressed in particular subsets of neurons being located on the cytoplasmic face of the plasma membrane in synaptic terminals and throughout the axon. It forms a stable ternary "Trans-SNARE" complex with two other exocytotic proteins, syntaxin and the synaptic vesicle protein synaptobrevin, which are essential for Ca^{2+}-regulated exocytosis, therefore regulating presynaptic vesicle trafficking and synaptic secretion and being directly involved in the release of neurotransmitters [42]. Based on the studies of different SNAP-25 polymorphisms in patients with schizophrenia, the integrity of SNAP-25 was

shown to be associated with clinical response [91], weight gain during antipsychotic treatment [91, 92], and executive functioning [138]. SNAP-25 was reported to be elevated in CSF of patients with schizophrenia ([143, 144]; Table 5) suggesting possible dysfunction of the synaptic secretion due to altered release of dopamine, serotonin, and glutamate [27]. These reported changes in the plasma membrane may also be in line with the above-mentioned assumption of the phospholipid dysfunction in schizophrenia, as reflected by alterations in the expression level of apolipoprotein A-IV, apolipoprotein E, and apolipoprotein A1.

Summary and conclusion

Initial studies on CSF in patients with schizophrenia revealed impaired brain–blood permeability with elevated total protein content and increased CSF/serum ratio for albumin. In some patients, intrathecal production of immunoglobulins was observed. In search of more specific biomarkers, metabolic, inflammatory, glial, neuronal, and neurotrophic mechanisms associated with schizophrenia were investigated [47, 104, 130]. Analyses of metabolites in CSF suggest alterations within glutamatergic neurotransmission as well as monoamine and cannabinoid metabolism. Increased cytokine levels in subgroups of patients with schizophrenia indicate a possible pathogenetic role of inflammatory, neuroimmunologic, and neurodevelopmental processes. Decreased levels of BDNF and NGF reported in recent CSF studies suggest a dysregulation within neuroprotective and neurodevelopmental pathways in first-episode patients with schizophrenia. So far, no changes of neuronal markers such as tau protein and neuron-specific enolase are reported, making major neuroaxonal damage in schizophrenia unlikely. CSF "metabolome" and "proteome" analysis in recent years revealed increased levels of glucose and VGF23-62 peptide and decreased levels of lactate and transthyretin.

Still, the discovery of "potential biomarker candidates" (PBC, [81]) or even disease-specific biomarkers in schizophrenia is at the very beginning. This could at least partially be a consequence of the heterogeneousness with regard to age, gender, medication, subtype, and duration of schizophrenia in groups of patients included by the majority of existing studies. The comparability of studies is further impeded by methodological heterogeneity. Only few CSF studies compared schizophrenia with other mental disorders such as bipolar or depressive disorders, which limits assessment of specificity of the reported CSF changes in schizophrenia. Given the additional methodological problems of proteomic procedures including a high vulnerability to outside influences like conditions of CSF collection and storage [118], the comparability of the various studies seems to be low and their relevance, therefore, questionable. A more integrated and more profound understanding of the relationship between the single parameters and their pathophysiological impact is mostly missing, and present findings must be considered as non-specific.

A number of steps appear to be necessary in order to bring forward the research of CSF in schizophrenia. In view of schizophrenia being a highly heterogeneous disease, a careful selection of patients to achieve homogenous cohorts is necessary. The older findings concerning the total cell count, the Blood-CSF barrier, and the immunoglobulins derive from investigations that used inconsistent and to some extent obsolete methodology with regard to the patients selection and the CSF analyses, are difficult to replicate nowadays, and must be considered, particularly with regard to the recent methodology improvements, with caution. One method to come forward could be to capture the psychopathology on a syndrome level by registering subscores for paranoia, disorganization, cognitive deficits, or negative symptoms such as anhedonia or listlessness (e.g., within "Positive and Negative Syndrome Scale", PANSS). A more profound characterization of the particular psychopathological profiles would allow analyses between single parameters and distinct psychopathological entities, alleviating comparison between different patient cohorts. The investigation of patients in the prodromal phase or within the first episode of schizophrenia would promote longitudinal investigations, which are still lacking, although they represent the only way to identify the prognostic impact and test the suitability of potential biomarkers.

Also regarding proteomics, rigorous adherence to standard procedures based on international CSF guidelines [87, 141] is necessary to improve the quality of proteomic studies and to allow frequently and more precise detection of possible marker candidates, preferably within multicenter projects in order to increase the number of patients included. The search for single proteins at different molecular sizes should be advanced, paving the way for identification of syndrome-specific biomarker candidates, and possibly making a step toward improving diagnosis, treatment, and monitoring of schizophrenia in the future by CSF analyses.

Conflict of interest The authors declare that they have no conflict of interest.

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