CSF-studies in neuropsychiatric disorders

Thomas J. Raedler & Klaus Wiedemann

University Hospital Hamburg-Eppendorf, Department of Psychiatry, Martinistr. 52, 20246 Hamburg, Germany.

Correspondence to: Thomas J Raedler, MD
University Hospital Hamburg-Eppendorf
Dept. of Psychiatry
Martinistr. 52, 20246 Hamburg, GERMANY
TEL. +49-40-42803-2210
FAX +49-40-42803-8072
EMAIL: traedler@uke.uni-hamburg.de

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Abstract

Cerebrospinal fluid (CSF) is a clear and colourless fluid that surrounds the brain and spine. Due to the close proximity of CSF to the brain, pathological brain-processes are likely to be reflected in CSF. CSF can be obtained through lumbar puncture and is frequently performed in the differential diagnosis of neuropsychiatric disorders. Beyond clinical applications, CSF has been studied as part of different research-protocols.

In this review, we will focus on CSF-analysis in Alzheimer Disease, major depression and schizophrenia. We will review both clinical applications as well as research applications in all three disorders. We will also assess new technological advances that have made it possible to study large numbers of proteins in CSF and how these advances may change CSF-analysis in the years to come.

Introduction

Cerebrospinal fluid (CSF) is a clear and colourless liquid that surrounds the brain and the spine. CSF serves as a mechanical protection of the brain and also carries nutrients and waste. CSF is continuously produced primarily in the choroid plexus of the cerebral ventricles at a rate of 0.3 ml/min with a decrease in CSF-production with increasing age [56]. With a total volume between 80–150 ml, CSF is replaced approximately three times per day. Due to the close connection between brain and CSF, pathological brain-processes are more likely to be reflected in CSF than in other body-fluids (e.g. blood or urine).

CSF has the advantage of being directly accessible for further evaluation through lumbar puncture. CSF-analysis is frequently performed in the differential diagnosis of neurological and psychiatric disorders. During the course of a lumbar puncture, a spinal needle is introduced under sterile conditions between the spinal processes of L4 and L5. Following the piercing of the dura, cerebrospinal fluid can be collected. Lumbar punctures are a safe and well tolerated procedure if performed by an experienced physician. Post puncture headaches are a possible complication of lumbar punctures. However, post puncture headaches occur less frequently in patients over 60 years [88]. Post punc-

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ture headaches are even less frequent in subjects who are referred for work-up of cognitive dysfunction [10].

CSF contains sugars, lipids, electrolytes and proteins with most constituents present in similar or lower concentrations than in blood [7]. So far, the analysis of CSF focuses on cellular elements and immunoglobulines as well as the total content of glucose and protein. First studies of CSF-proteins date back to the early 1980ies [34]. Since then, only few studies have focused on the composition of proteins in CSF. In studies of CSF-proteins, only tubes made out of polypropylene should be used to avoid a deposition of the proteins on the wall of the test tubes [9]. The average protein-concentration in CSF is around 250 mg/l. Protein-concentrations are the highest in the first CSF-samples collected and decrease with ongoing sampling [8]. Over 70% of the CSF-proteins are isoforms of albumin, transferrin and immunoglobulines [5]. The entry of proteins into the CSF is restricted through the blood-CSF-barrier that is formed primarily through brain capillaries. The blood-CSF-barrier leads to lower protein-concentrations in CSF compared to blood. The intactness of the blood-CSF-barrier can be assessed through the ratio of CSF-albumin to serum-albumin [28], as albumin is only synthesized in the liver. Age-corrected reference-ranges exist for the ratio of CSF-albumin to serum-albumin [71] that is more stable among subjects under the age of 45 years than among older subjects [7]. Under certain pathological conditions (e.g. MS and autoimmune disorders), immunoglobulins are synthesized in the CNS as an expression of a local pathological immune response [77]. The IgG-index serves as a measure of the intrathecal production of IgG and corrects for possible changes in the blood-CSF-barrier by dividing the CSF-IgG to serum-IgG ratio by the CSF-albumin to serum-albumin ratio [7].

Recent technological advances have made it easier to analyse proteins in CSF [17, 23, 81, 103]. An enormous wealth of information might be present in the less abundant CSF-proteins (10–1000 fmol/µl), which are likely to contain disease-specific information for different neuropsychiatric disorders. Due to technical limitations, the identification of these less abundant CSF-proteins had not been possible until recently [22].

In this review we will focus on the role of CSF-analysis in three neuropsychiatric disorders (Alzheimer Disease, major depression and schizophrenia). While CSF-analysis is routinely performed in Alzheimer Disease and carries diagnostic value, CSF-analysis in schizophrenia and major depression serves primarily for the exclusion of other pathological conditions (e.g. infectious or inflammatory disorders). Besides the clinical evaluation of CSF, research on CSF has been actively pursued in all three disorders. In addition, we will also review possible future applications of CSF-analysis, which may change CSF-analysis in the years to come.

Alzheimer Disease

Alzheimer Disease is the most frequent form of dementia, which affects increasing number of patients world-wide, as the world-population is growing older. It is estimated that about 16 million patients suffer from Alzheimer Disease world-wide. The diagnosis of Alzheimer Disease is based on a typical clinical presentation and time-course as well as the absence of other forms of dementia. The diagnostic work-up for dementia includes a detailed history from patients and caregivers as well as a physical examination, brain-imaging studies, a laboratory assessment and a lumbar puncture. A definite diagnosis of Alzheimer Disease can only be established post mortem and is based on the presence of amyloid plaques and microtubuli-associated tau-protein that form the neuropathological hallmarks of Alzheimer Disease [20].

Biomarkers can be used to diagnose neuropsychiatric disorders as well as to assess treatment-effects. Different proteins have been evaluated as potential biomarkers for Alzheimer Disease. Over the past few years, the focus has been on β-amyloid and tau-protein. β-amyloid is a component of the amyloid (senile) plaques and microtubuli-associated tau-protein is closely related to neurofibrillary tangles. Tau-protein is located in the axons of neurons. Tau-protein exists in six different isoforms and has different phosphorylation sites. In Alzheimer Disease, tau-protein is abnormally phosphorylated and aggregates into paired helical filaments [54]. The total concentration of tau-protein is a state-marker of illness and reflects the intensity of neuronal degeneration in Alzheimer Disease as a neurodegenerative disorder. Tau-levels in the CSF were increased about three-fold in Alzheimer Disease in different studies [e.g. 42, 43]. On the other hand, normal concentrations of tau-protein are found in several other neuropsychiatric illnesses (e.g. depression and Parkinson's Disease), that are included in the differential diagnosis of Alzheimer Disease.

The other potential biomarker for Alzheimer Disease is β-amyloid, the major component of senile plaques. β-amyloid is the result of proteolytic cleavage of the amyloid precursor protein (APP) through β-secretase and γ-secretase. Two major variants of β-amyloid exist with either 40 ($A\beta_{1\text{-}40}$) or 42 ($A\beta_{1\text{-}42}$) amino acid residues. Multiple studies found β-amyloid levels to be decreased by approximately 50% in the CSF in Alzheimer Disease [e.g. 1, 27, 59]. This decrease of β-amyloid concentrations in CSF in Alzheimer Disease is most likely due to a deposition of β-amyloid in the senile plaques.

Changes in tau protein-levels and β-amyloid-levels in CSF show good sensitivity and specificity for Alzheimer Disease. Both assays have also been used in combination as a tool to diagnose Alzheimer Disease [41] as well as for the differential diagnosis of dementia [89]. Both proteins have proven helpful to identify patients with mild

cognitive impairment, who will go to develop Alzheimer Disease [2, 37].

Sunderland performed a meta-analysis on data from 4500 Alzheimer patients and healthy controls. This meta-analysis confirmed the above-mentioned differences in CSF between Alzheimer Disease and healthy controls (increase in tau-protein and decrease in β-amyloid in Alzheimer Disease), suggesting that these proteins could be used as bio-markers. Sunderland also studied β-amyloid$_{1-42}$ and tau protein-levels in CSF in a sample of 131 patients with Alzheimer Disease and 73 controls. In this sample, CSF-levels of β-amyloid$_{1-42}$ were significantly lower in Alzheimer Disease. On the other hand, levels of CSF-tau protein were signicantly higher in Alzheimer Disease. Using a cut-off for both CSF β-amyloid$_{1-42}$ and CSF-tau protein resulted in a sensitivity of 92% and a specificity of 89% for the distinction between Alzheimer Disease and healthy controls [82].

Abnormal phosphorylation of tau-protein plays a major role in the pathogenesis of Alzheimer Disease [54]. The phosphorylation of the tau-protein at different epitopes was also evaluated as a biomarker in Alzheimer Disease and other dementias. The levels of tau-protein phosphorylated at different epitopes helped to differentiate Alzheimer Disease from patients with Lewy Body Dementia and frontotemporal dementia [12, 36, 43], mild cognitive impairment [11] as well as major depression [13].

Amyloid-β-derived diffusible ligands (ADDLs) are smaller and soluble oligomers of β–amyloid peptides. ADDLs have been hypothesized to be the causative agent for memory loss in Alzheimer Disease [48], as soluble abeta oligomers may cause synaptic failure [49]. Using different methods, significantly elevated ADDL-levels were found in the frontal cortex [35] as well as in the CSF of patients with Alzheimer Disease [30] compared to healthy controls. In another study, however, levels of soluble amyloid precursor protein (sAPP) in the CSF did not differ between Alzheimer Disease and healthy controls, while the levels were elevated in patients with mild cognitive impairment [65].

Several other proteins besides tau-protein and β-amyloid were also studied in Alzheimer Disease. Increased levels of α_2-haptoglobin were found in the CSF of patients with Alzheimer Disease [45, 18]. Another study reported several proteins altered in the CSF of patients with Alzheimer Disease including proapolipoprotein, apolipoprotein E, β-microglobulin, retinolbinding protein, transthyretin and ubiquitin [25]. Frontotemporal degeneration (FTD), one of the most common types of dementia, is part of the differential diagnosis of Alzheimer Disease. Several proteins were identified that can be used to distinguish Alzheimer Disease from frontotemporal dementia [24].

SELDI-TOF is a new analytical method that combines a surface-enhanced laser desorption with ionization-time of flight technology. Using SELDI-TOF, Cystatin C, a cystein protease inhibitor protein with a mass of 13.4 kDa was identified as a potential biomarker for Creutzfeldt-Jakob Disease, the most common prion disease in humans [74]. Using the same technology in Alzheimer Disease, Cystatin C and four additional proteins were identified, that differentiated CSF from patients with Alzheimer Disease from healthy controls [17]. However, these markers need to be confirmed in larger clinical samples.

Affective Disorders

Total protein levels in CSF were elevated in unipolar and bipolar depressed males but not in depressed women [73]. This finding of a significant elevation of total CSF-protein levels in male depressed patients was confirmed in a second sample [66].

The role of different monogenic amines and the HPA-axis (hypothalamus – pituitary gland – adrenal gland) has been the focus of research in depression for the past decades. No differences were found in the levels of norepinephrine (NE) and the main metabolites of serotonin (5-HIAA – 5-hydroxyindolacetic acid) and dopamine (HVA – homovanillic acid) in CSF between healthy controls and depressed patients. However, an alteration was found for the interaction between the noradrenergic and the serotonergic system in the depressed patients [32]. In a different clinical sample, depressed subjects showed a significant increase of norepinephrine-levels in CSF [101].

Studying depressed patients with comorbid psychiatric disorders, depressed subjects with a history of alcoholism had lower CSF-levels of HVA than healthy controls, while the CSF-levels of depressed subjects without a history of alcoholism were higher [80]. Depressed patients with comorbid PTSD also had higher CSF-levels of HVA than depressed patients without PTSD or healthy contols. Levels of the serotonin-metabolite 5-HIAA and the norepinephrine-metabolite MHPG (methoxyhydroxyphenylglycol) did not differ between these groups [79].

Glutamine-levels in CSF were significantly elevated in unmedicated depressed patients compared to healthy controls, suggesting changes in the glutamate system [51]. Changes in the thyroid function are frequently associated with depression. CSF TRH-levels were markedly increased in depressed patients compared to patients with somatization disorder and peripheral neurological disorders [3].

Neuropeptide Y (NPY) is another neuropeptide that has been associated with depression. Neuropeptide Y-levels in CSF were significantly decreased in depression, while monoamine metabolites showed no differences in this

sample [39]. Neurotensin 3 (NT-3), a member of the neurotrophins, enhances the survival of neurons and has also been studied in depression. In elderly patients with major depression, NT-3 levels in CSF were significantly elevated when compared to both healthy controls and patients with Alzheimer Disease [40].

With regards to changes in the HPA-axis, increased cortisol-levels in plasma are a consistent finding in depressed patients. Peripheral cortisol-levels are regulated by CRF (Corticotropin Releasing Factor)- and ACTH (corticotropin)-levels in the brain. Despite the peripheral hypercortisolism, ACTH- and CRF-levels in the CSF were in the normal range in depressed patients [101]. CRF also failed to differ between unmedicated depressed patients and healthy controls in another study. However, early life stress predicted significantly lower CRF-concentrations in CSF [16]. The CSF-levels of the neuroactive steroid pregnenolone were significantly lower in depressed patients than in healthy controls [31]. The concentration of another neurosteroid 3α-5α-ALLO was about 60% lower in the CSF from patients with major depression, while other neurosteroids did not differ from normal controls. Treatment with the antidepressants fluoxetine and fluvoxamine normalized the levels of this neurosteroid in CSF [85].

Looking at cytokines, the proinflammatory cytokine interleukin 6 (IL-6) has been associated with changes in depression. However, no differences were found in CSF-concentrations of IL-6 in a sample of depressed patients and matched healthy controls [14]. In another sample of patients, higher levels of the cytokines IL-1 and IL-6 were found in depressed patients, while TNFα did not differ [50].

CSF-studies can also be used to monitor treatment-effects in depression. Treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram resulted in a significant increase of HVA as well as a significant decrease of 5-HIAA in the CSF of subjects with major depression [61].

Electroconvulsive treatment (ECT) is another treatment-option for major depression. CSF was collected from depressed subjects before and after a course of six ECT treatments. The CSF / serum ratio for albumin as a measure of the blood-brain-barrier was unchanged after the course of ECT. Similarly, different markers for neuronal and glial degeneration (tau protein, neurofilament and S-100 beta protein) did not change during the course of ECT. These results suggest that no neuronal or glial damage occurs during a course of ECT [104].

Vagus nerve stimulation (VNS) is a novel treatment for epilepsy. In epilepsy, VNS results in changes in monamine- and GABA-concentrations in CSF [4]. VNS has also been used as a potential treatment of depression. While the CSF-concentrations of HVA, the main metabolite of dopamine, increased after VNS, the concentrations of all other monoamines and GABA remained unchanged [15].

Suicide and suicide-attempts are frequently associated with major depression, but also occur in other psychiatric disorders. In a sample of patients who were admitted after a suicide-attempt, low CSF 5-HIAA levels predicted a suicide within the following year [64]. Looking at the relationship between aggressivity and depression and monoamines in CSF, low 5-HIAA levels in CSF correlated with higher aggressivity and more dangerous suicide attempts in subjects with major depression [68]. Insulin-levels in CSF were measured in patients who had attempted suicide. No differences were found between patients with and without a diagnosis of major depression. Comparing the method of the suicide attempt itself, subjects with violent suicide-attempts had higher CSF-insulin levels than those patients who had used nonviolent means [94]. At the same time female suicide-attempters with a history of major depression had significantly lower CSF-leptin levels than those without a history of major depression [95].

CSF-studies were also used to assess the effects of trypophan on serotonin-synthesis. Tryptophan is a precursor for serotonin, one of the major neurotransmitters implicated in depression. Tryptophan-levels and 5-HIAA-levels in CSF show marked diurnal variations [47]. Serotonin-levels can be reduced through dietary interventions such as a tryptophan-depleted amino-acid drink (tryptophan-depletion). Tryptophan depletion leads to a marked decrease in both CSF-tryptophan and CSF-5-HIAA [98]. In clinical studies, tryptophan-depletion frequently results in a temporary recurrence of depressive symptoms in depressed patients in remission. Using continuous CSF-sampling during tryptophan-depletion, a threshold was found for CSF tryptophan-levels that predicted the recurrence of depressive symptoms [72].

Schizophrenia

Lumbar punctures are frequently performed in the differential diagnosis of schizophrenia, in particular in patients with new onset schizophrenia as well as clinically unclear cases. Lumbar punctures serve to exclude other disorders that may also present with similar clinical features.

CSF-studies were performed in schizophrenia in different clinical samples to assess the levels of neurotransmitters in schizophrenia. Schizophrenic subjects had significantly lower HVA-levels in CSF than healthy controls, while 5-HIAA-levels did not differ. The persistence of a low HVA / 5-HIAA ratio after antipsychotic treatment correlated with a poorer clinical outcome after 5 years [97]. In a sample of unmedicated first-episode schizophrenic patients, no differences were found in the levels

of biogenic amines and their metabolites compared to healthy controls [57]. In a large sample of schizophrenics, CSF-levels of HVA did not differ from healthy controls [6]. Unmedicated schizophrenics had a significantly higher glutamine to glutamate-ratio in CSF, suggesting a dysregulation in the glutamate-cycle in schizophrenia [38].

CSF-studies also served to assess the effects of antipsychotic treatment on monoamines. Treatment with the atypical antipsychotic olanzapine significantly increased the concentration of the dopamine metabolite HVA (homovanillic acid) as well as the ratio of HVA to 5-HIAA, the main serotonin metabolite. However, these changes were unrelated to the clinical efficacy of olanzapine [75]. CSF-levels of HVA decreased significantly after withdrawal of antipsychotic medication [6]. In a sample of patients with onset of schizophrenia during childhood, six weeks of treatment with haloperidol or clozapine did not change CSF monoamine concentrations or the ratios of HVA to 5-HIAA or MHPG [44].

Schizophrenia is frequently associated with the use of cannabis. Ongoing use of cannabis is a risk-factor for a worse clinical prognosis in schizophrenia. Until now, the links between schizophrenia and cannabis remain unclear. Anandamide is a naturally occurring endocannabinoid, which activates cannabinoid receptors. Anandamide-levels in CSF are significantly elevated in untreated first-episode schizophrenics compared to healthy controls or patients suffering from dementia or affective disorders. At the same time, anandamide levels are negatively correlated with the severity of positive symptoms in unmedicated subjects [33].

The infectious theory of schizophrenia postulates an infectious etiology for schizophrenia. While no single infectious agent has been identified, different virus and bacteria have been implicated. In the CSF of unmedicated schizophrenia with recent onset, increased levels of IgG antibodies were found against toxoplasma gondii, cytomegalovirus and human herpesvirus type 6. In treated schizophrenics, the levels of these antibodies did not differ from healthy controls [52]. At the onset of a psychotic episode, the proportion of macrophages was significantly higher in the CSF of schizophrenic patients. During antipsychotic treatment, the proportion of macrophages returned toward normal [62]. The CSF from acutely psychotic patients with schizophrenia also has significantly more activated lymphocytes and a decreased number of normal small lymphocytes [63].

Cytokines are proteins that are secreted by inflammatory leukocytes and act as intercellular mediators. Cytokines can have both stimulating and suppressing effects on the immune system. Different cytokines were analysed in the CSF in schizophrenia. Compared to healthy controls, IL-6 levels were significantly higher in the serum of schizophrenic patients, while the differences failed statistical significance in CSF [86]. IL-1- and IL-2-levels did not differ between medicated schizophrenic subjects and healthy controls [70]. Licinio, on the other hand, found higher IL-2- but not IL-1-levels in neuroleptic-free schizophrenic subjects [53]. Garver found significantly different levels of the pro-inflammatory cytokine interleukin-6 (IL-6) in the CSF of two groups of schizophrenics, who differed in their response to antipsychotic treatment. The authors concluded that at least one subtype of schizophrenia was associated by a central immune process [29].

Assessing the intactness of the blood-brain-barrier in schizophrenia, Schwarz et al. reported an impairment of the blood–CSF-barrier in schizophrenia that was linked to an increase in sICAM-1, a marker for inflammatory processes [78]. In another clinical sample, a disturbed blood-brain-barrier was found in 19% of schizophrenic subjects [60].

Different proteins were studied in the CSF of patients with schizophrenia. Increased levels of CSF tau protein levels are associated with Alzheimer Disease and other neurodegenerative disorders. Tau protein levels as well as phospho-tau levels in CSF did not differ between schizophrenics and healthy controls [76], arguing against the concept of schizophrenia as a neurodegenerative disorder.

Changes in ACE (Angiotensin-Converting Enzyme)-levels have been associated with schizophrenia in particular in patients with predominant negative symptoms and polydipsia. Drug-free schizophrenic subjects had significantly lower ACE-levels in CSF compared to schizophrenic subjects who were treated with antipsychotics [92]. ACE levels in CSF but not in serum correlated significantly with the duration of the schizophrenic illness as well as the duration of the current episode. No similar correlation was found for ACE-levels in serum [93].

Several proteins that are involved in the organization of the brain as well as synaptic function were also assessed in schizophrenia. Neural cell adhesion molecule (N-CAM) is a cell-recognition molecule that plays a role in brain-organization and –development. N-CAM is expressed in four different isoforms. CSF-N-CAM levels were significantly lower in first episode schizophrenics, who had been treated with antipsychotics, but not in untreated first-episode patients [91]. In another study, CSF N-CAM levels were significantly increased in schizophrenia compared to healthy controls, while antipsychotic treatment did not have an effect on the levels of N-CAM [87]. In monocygotic twins discordant for schizophrenia, CSF N-CAM levels were significantly increased in the affected twin. At the same time, CSF N-CAM levels did not differ from healthy controls in the unaffected twin [69]. N-CAM VASE, a 10 amino-acid insertion into the N-CAM molecule, was significantly

elevated in the CSF of schizophrenic subjects, but not in bipolar subjects or healthy controls [90].

SNAP-25 is a synaptosomal protein that plays a major role in exocytosis. In a first study, CSF SNAP-25 levels were significantly increased in schizophrenia compared to healthy controls and headache patients. However, CSF SNAP-25 levels did not differ between schizophrenic and bipolar patients [84]. Compared to healthy controls, SNAP-25 levels were increased in another study in CSF in schizophrenia both after treatment with haloperidol as well as after treatment with placebo [83].

Switching to a different technology, micrometer-sized spherical particles of unknown origin and function can be found in the CSF with scanning electron microscopy. These micrometer-sized spherical particles of unknown origin and function were found significantly more frequently in the CSF of subjects with schizophrenia compared to healthy controls [96]. However, these results were not replicated in a second study, which failed to find different amounts of these particles in the CSF from patients with schizophrenia and healthy controls [26].

New applications of CSF-analysis

Different approaches have been used to study the composition of proteins in neuroscience [19]. Mass spectrometry (MS) is a recently developed method that depends primarily on the molecular mass of a protein. Mass spectrometry can identify small modifications in proteins and can be used to identify the primary structure of a protein. Electro spray ionization mass spectrometry (ESI MS) and matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) as well as surface-enhanced laser desorption/ionization mass spectrometry (SELDI MS) are among newer technological modifications of mass spectrometry that contributed to the recent success of mass spectrometry [21]. Modern developments of these technologies make it possible to study large amounts of proteins in different biological tissues, including CSF.

Proteomics

Proteomic studies offer a new approach to the study of proteins in different body-fluids. This approach may be particularly suitable for use in psychiatric disorders [67]. Recently new technologies were applied to analyse proteins and peptides in body-fluids on a general scale [19, 55]. Different post-translational modifications can occur after the assembly of the amino acid sequence in the ribosomes. Posttranslational modifications include changes in the structure of the protein through protein-folding and the attachment of functional groups, such as acetate, phosphate, lipids and carbohydrates. In addition, enzymes can remove amino acids from the end of the polypeptide-chain or cut the polypeptide-chain. These modifications can alter the structure and function of proteins significantly. Compared to genetic studies, studies of CSF-proteins have the advantage that they allow an assessment of posttranslational modifications of protein-synthesis.

Different applications of proteomics include studies of the expression of proteins (expression proteomics), comparison between healthy and diseased states (comparative proteomics), the structure of proteins (structural proteomics) as well as interactions between different proteins (functional proteomics). New technologies allow a rapid through-put and fast screening of a large number of proteins in a biological tissue. This proteomic approach may offer a valid approach to diagnosis of disorders as well as a better understanding of pathophysiology.

Several new methods have made proteomic studies of CSF possible [102]. Combining capillary electrophoresis with mass spectrometry resulted in a new diagnostic tool that was initially applied to the analysis of protein patterns in urine [99, 58]. This method allows the automated analysis of polypeptide patterns in body fluids [46]. This method was recently applied to the analysis of CSF and currently allows the identification of 450 different polypeptides in CSF [100]. Preliminary data suggests that this method reveals specific protein patterns for both Alzheimer Disease and schizophrenia (Raedler, manuscript submitted).

Conclusion

For many years, CSF-analysis has played a major role in the clinical work-up of neuropsychiatric disorders. Compared to other body-fluids, CSF has the advantage of a close proximity to the brain. Therefore, pathological brain-processes are more likely to be reflected in CSF than in other body-fluids.

Tau-protein and β-amyloid as well as phosphorylated tau-protein are potential CSF-biomarkers for Alzheimer Disease. These bio-markers are well established, while other biomarkers for Alzheimer Disease (e.g. soluble amyloid oligomers) are still under investigation. Based on the currently available biomarkers, CSF-analysis plays a role in the differential diagnosis of Alzheimer Disease. As new technologies have become available, future research will show in how far the existing biomarkers can be improved and if CSF-biomarkers exist to monitor treatment in Alzheimer Disease.

In depression, CSF-analysis has focused mainly on biogenic amines and neurotransmitters. The currently available literature shows heterogeneous results, which may reflect the heterogeneous etiology of depression. Future CSF-studies using modern analytical technologies may help to identify different subtypes of depression as well as potential biomarkers for treatment-response.

In schizophrenia, CSF-analysis also plays a limited clinical role beyond differential diagnosis. Studies of neurotransmitters, cytokines and synaptic proteins in CSF have shown conflicting results. Again, different clinical features (acuity of psychosis, subtype, treatment-status) may result in diverging results.

Up until now, CSF-analysis has been limited to cell-count, analysis of immunoglobulines as well as total content of glucose and protein. In addition, selected CSF-proteins have been analysed in smaller patient-cohorts. New advances in the methodology of CSF-analysis have made it possible to identify large numbers of proteins at a very low concentration. These technologies may lead to a break-through in the CSF-analysis and may result in new biomarkers for disease as well as treatment-response.

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