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Has the time arrived for cerebrospinal fluid biomarkers in psychiatric disorders?

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ABSTRACT

Psychiatric disorders are currently classified, in the majority of cases, by clinical syndromes. However, advances over the last decade in imaging and biochemical biomarkers in several Central Nervous System (CNS) disorders anticipate the incorporation of some of these markers in the diagnostic work-up of psychiatric conditions. In particular, CSF biomarkers offer the possibility of detecting a wide range of pathophysiological processes in the CNS. Newer CSF markers can measure axonal and synaptic damage, glial activation, and oxidative stress in CNS disorders with high precision. The possibility that these markers can be applied in the differential diagnosis of common psychiatric disorders such as Schizophrenia, Major Depressive or Bipolar Disorders not only to rule out neurodegenerative diseases but also to identify specific biomarker signatures has yet to be explored. In particular, synaptic proteins in CSF could be useful as markers of synaptic and neurotransmitter transmission impairment since these are key molecular features of psychiatric conditions. In this paper we outline the current and potential applications of CSF biomarkers in psychiatric disorders.

1. Introduction

Psychiatric disorders are currently classified predominantly by clinical syndromes that are distinguished by the predominant symptoms, their severity, duration, and potential causes [1]. When psychiatric conditions are believed to be due to a specific causal agent, such as a medical condition or toxic agent, they are usually considered secondary disorders and if there is currently no detectable causal agent, the disorder is then considered idiopathic [1]. These classifications are, however, arbitrary, and it is expected that they will change as the knowledge about the molecular pathobiology of these conditions advances.

Progress in biochemical or imaging biomarkers during the last decades have led to enormous advances in diseases of the Central Nervous System (CNS). In particular, in Alzheimer's disease (AD) and in other neurodegenerative diseases, there has been a conceptual transition from a clinical-pathological definition to a biological framework [2,3]. In this new scenario, biomarkers play a major role in the characterization of different disease stages in clinical practice and in clinical trials [4].

Cerebrospinal fluid (CSF) biomarkers offer the possibility for detecting many pathophysiological processes in the CNS simultaneously at a relatively low cost compared to Positron Emission Tomography (PET) imaging. In addition, CSF offers a more dynamic measure of a brain disorder since this biofluid reflects the state at a given point while imaging techniques reflect the cumulative change.

The use of CSF biomarkers in clinical practice in CNS disorders such as AD and multiple sclerosis (MS) is well established. In AD, several studies have consistently identified a specific CSF biomarker signature of three core AD biomarkers, namely low levels of amyloidβ-$_{42}$ ($A\beta_{42}$) and high levels of total tau (t-tau) and phosphorylated tau (p-tau), that reflect the main neuropathological hallmarks of the disease [3,5]. In addition, there is evidence that the CSF ratio $A\beta_{42}/A\beta_{40}$ is superior to $A\beta_{42}$ alone regarding diagnostic validity and reliability [6–9]. CSF

Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; *APOE*, apolipoprotein E; CSF, Cerebrospinal fluid; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, Mild cognitive impairment; MMSE, MiniMental State Examination; NfL, Neurofilament-light; SCD, subjective cognitive decline

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biomarkers in AD play a major role in clinical practice by increasing diagnostic accuracy and in clinical trials by improving selection of patients in the early disease stage, and ensuring adequate drug target engagement [3,4]. Other newer CSF biomarkers have been investigated in multiple neurodegenerative diseases. As a marker of axonal damage, neurofilament-light (NfL) levels are elevated in many neuropsychiatric disorders early in the disease and correlate with disease progression and brain atrophy in AD, MS, Frontotemporal dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) among others [3,10,11]. Other newer markers include a group of synaptic proteins in CSF. More than a dozen synaptic proteins have been characterized in CSF in AD and other neurodegenerative diseases [12–19] as a measure of early and prominent synapse loss observed in many neurodegenerative diseases [20]. In AD, the levels in CSF of the synaptic protein neurogranin change early in the disease course and correlate with clinical measures of cognition [16,21]. Finally, different inflammatory markers have also been investigated in neurological disorders and some, such as YKL-40, seem to also correlate with disease progression in some neurodegenerative conditions [11,22]. Despite the many studies supporting the utility of CSF biomarkers in neurological disorders, whether some of these markers can also be informative in non-neurodegenerative psychiatric disorders remains unclear. There are many research studies investigating different CSF markers in conditions such as schizophrenia, major depressive disorder (MDD) or bipolar disorder (BD), although only few studies have investigated newer markers and, to-date, none have been incorporated into clinical routine.

This manuscript was an initiative that arose from a discussion within the Society for CSF analysis and clinical neurochemistry (http://www.neurochem.info/) [23]. In this article we review the published evidence on CSF biomarkers in non-neurodegenerative psychiatric disorders and outline the potential applications of newer markers in these conditions. We searched the PubMed database for papers using the terms “schizophrenia”, “bipolar”, “depressive”, “psychiatric”, and “CSF” or “biomarkers”.

2. Current use of CSF biomarkers in psychiatric conditions

The use of CSF biomarkers in clinical practice in psychiatric conditions is usually limited to those cases in which an underlying secondary cause is suspected. For example, a patient with sudden onset of psychotic symptoms may undergo CSF examination to rule out a CNS infection or to detect antibodies associated with antibody-mediated encephalitis [24]. Encephalitis due to antibodies directed against the glutamate NR1 subunit of the *N*-methyl-D-aspartate glutamate receptors (NMDAR) can lead to psychosis and/or other psychiatric symptoms similar to those in schizophrenia or other psychiatric conditions [24]. Other autoantibodies can also lead to similar clinical syndromes [24] and CSF examination may help in the differentiation of the underlying cause.

In addition, some neurodegenerative diseases, such as AD, FTD and dementia with Lewy bodies (DLB), can present with neuropsychiatric symptoms mimicking idiopathic psychiatric disorders [25]. A typical example is DLB, a neurodegenerative condition in which visual hallucinations and delusions are core elements. In this scenario, it can be particularly challenging to distinguish between an idiopathic psychiatric condition and a neurodegenerative condition presenting with neuropsychiatric symptoms. In these situations, CSF biomarkers (e.g. $A\beta_{42}/A\beta_{40}$, t-tau and p-tau) may help to rule out these neurodegenerative disorders. A recent multicenter study performed in memory clinics showed that up to 20% of patients presenting clinically with affective and/or psychotic symptoms had a CSF AD profile and the finding led to a change in the primary diagnosis in all cases [26]. Although this study was not performed in a psychiatric setting, it supports the potential use of CSF biomarkers to detect AD in some elderly patients with behavioral presentations. CSF analyses can be also useful to support other alternative diagnoses. A patient with behavioral symptoms in whom FTD is suspected may show high CSF levels of NfL or YKL-40 that could support this diagnosis [10,27,28]. Unfortunately, despite these potential applications, CSF in psychiatric clinics is used only in a few countries within Europe as part of the clinical diagnostic work-up.

3. Research studies of CSF biomarkers in affective and psychotic psychiatric disorders

Although the use of CSF biomarkers in clinical routine in affective and psychotic disorders is very limited, several research studies have examined CSF biomarkers in these disorders.

Many studies have investigated CSF biomarkers in BD. Despite the large number of studies, a systematic recent review only identified consistent data for monoamines, homovanilic acid (HVA) and 5-hydroxy-indoleactic acid (5-HIAA), both of which are elevated in BD [29].

Other studies have measured $A\beta_{1-42}$ levels in CSF in patients with MDD [30–32]. A recent meta-analysis found a marginally significant lower levels of $A\beta_{1-42}$and higher levels of isoprostane (a marker of oxidative stress) in CSF from patients with MDD [30]. The reason for the lower levels of $A\beta_{1-42}$ in MDD remains controversial but it could reflect an increase in amyloid pathology in MDD [33,34] or perhaps a decrease in Aβ production at synapses, reflecting the reduced number of synapses in the frontal cortex in MDD [35].

A recent meta-analysis of CSF markers in schizophrenia and affective disorders concluded that these disorders may have in common signs of brain blood barrier impairment [36]. In particular, an increase in the CSF/serum albumin quotient was increased in schizophrenia and affective disorders. In addition, IL-6 and IL-8 levels in CSF were increased in schizophrenia [36,37]. However, most studies were underpowered, did not include healthy controls and did not account for the use of psychotropic medication. In addition, the specificity of these changes and the potential applications in clinical routine remain unclear.

There is growing evidence that major psychiatric conditions, such as MDD and schizophrenia, show loss of synaptic spines and impairment of the synaptic and neurotransmitter machinery in the CNS [35,38]. A recent meta-analysis found a significant reduction in synaptophysin in the brain of patients with schizophrenia in the hippocampus, frontal and cingulate cortices [38]. Therefore, although there are still insufficient studies to evaluate which synaptic proteins are more impaired in each condition, CSF biomarkers could in principle be used for supporting the diagnosis of a specific psychiatric condition and possibly staging the disease. Two studies have shown that the altered levels of the SNARE protein, SNAP-25, in the brain of patients with schizophrenia maybe reflected by elevated levels of SNAP-25 in the CSF of schizophrenia patients [39,40]. However, CSF levels were not increased in a small study of patients with BD [39]. More studies are clearly needed to investigate the specificity of changes in these and other synaptic proteins across different brain regions in different disorders and their correlation with clinical measures.

Finally, other studies have used proteomics to investigate specific CSF profiles associated with each psychiatric condition [41–44].

4. Potential clinical value of CSF biomarkers in affective and psychotic disorders

CSF biomarkers could be used in idiopathic affective/psychotic disorders to (1) rule out secondary causes, mainly neurodegenerative diseases (2) to detect characteristic pathophysiological profiles associated to each condition (Table 1).

First, CSF markers may help in detecting neurodegenerative diseases that could either represent the main cause of the neuropsychiatric syndrome or a comorbidity with contribution to the clinical presentation. For example, high levels of NfL in CSF could represent a “red flag” that alerts the physician about potential secondary causes. Elevated NfL

Table 1
Potential clinical use of CSF biomarkers in psychiatric conditions.

Condition	Marker	Potential uses
Acute or subacute psychosis	Neuronal auto-antibodies	Rule out autoimmune encephalitis [24]
Psychosis or affective disorder	NfL	"Red flag" for neurodegenerative disease [10]
Psychosis or affective disorder	$A\beta_{1-42}$, or ratio $A\beta_{1-42}/A\beta_{1-40}$, tau and p-tau	Rule out AD [26]
Psychosis or affective disorder	Synaptic proteins	Diagnostic or prognostic value [39]

Abbreviations: Aβ: amyloid-β; AD: Alzheimer's disease; NfL: Neurofilament-light.

levels in CSF in a patient with first episode late-onset BD could be a sign of an underlying neurodegenerative dementia, such as AD or FTD. This trait could help the physician to assess whether further imaging tests such as Magnetic Resonance Imaging or ^{18}F- fluorodeoxyglucose (FDG)-PET are needed.

A more specific approach would be to use markers of synapse loss. It is clear that many more studies on synaptic proteins are needed, but one could anticipate that affective and psychotic disorders may show marked changes in synaptic proteins in CSF. Synaptic biomarkers may even be better suited for use in psychiatric syndromes due to the absence of widespread neurodegeneration that can be a confounding factor in interpreting neuronal protein levels in the CSF at late stages of neurodegenerative diseases [19].

One could speculate that depending on the type of disorder, a specific panel of synaptic proteins may be associated with the condition, and perhaps be useful in predicting prognosis or drug-response.

5. Conclusions

In summary, CSF markers have revolutionized the field of neurodegenerative disorders and some markers have shown diagnostic and prognostic value in clinical routine. It is expected that some of these newer markers will have application in the early and differential diagnosis of affective and psychotic disorders. In particular, NfL in CSF could be used as a "red flag" of an underlying neurodegenerative pathophysiology and synaptic proteins could be particularly useful as they may capture the key molecular events that characterize these disorders. In turn, research on CSF biomarkers in idiopathic affective/psychotic disorders could be valuable to rule out this etiology in patients with neurodegenerative disorders. This will help to refine the pathophysiological underpinnings of these intriguing conditions and possibly assist in finding better therapies.

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Conflict of interest statement

AL has served on scientific advisory boards of Fujirebio Europe, Eli Lilly, Novartis and Nutricia and is the inventor of a patent on synaptic markers in CSF (EP18382175.0).

LP has received honoraria as member of advisory boards from Fujirebio Europe, IBL International, Merck, Roche and Biogen.

OB is the inventor of a patent on synaptic markers in CSF (EP18382175.0).

JW has has received honoraria as member of advisory boards from Eli Lilly, Roche, Boehringer Ingelheim, Immungenetics, and MSD Sharp Dohme, and lecture fees from Janssen.

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