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REVIEW

Biomarkers in cerebrospinal fluid of patients with bipolar disorder versus healthy individuals: A systematic review

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Abstract
Background: The pathophysiological processes of bipolar disorder (BD) may be detectable by the use of cerebrospinal fluid (CSF) biomarkers.
Aim: We aimed for the first time to review studies of CSF biomarkers in patients with BD compared to healthy control individuals (HC). We investigated the effect of diagnosis, age, gender, clinical state, medication, technical characteristics of tests, fasting state and, cognitive function if applicable.
Method: We did a systematic review according to the PRISMA Statement based on comprehensive database searches for studies on cerebrospinal biomarkers in patients with bipolar disorder versus HC. Risk of bias was systematically assessed.
Results: The search strategy identified 410 studies of which thirty-four fulfilled the inclusion

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criteria. A total of 117 unique biomarkers were investigated, out of which 11 were evaluated in more than one study. Forty biomarkers showed statistically significant differences between BD and HC in single studies. Only the findings of elevated homovanillic acid and 5-hydroxyindoleacetic acid were replicated across studies. Most studies had a cross sectional design and were influenced by risk of bias mainly due to small sample size, lack of data on mood state at the time of the CSF puncture and not considering potential confounders including age, gender, diagnoses, BMI, life style factors such as smoking, and psychotropic medication.

Conclusion: Specific monoamine CSF biomarkers may be related to the pathophysiology of BD. Future studies must aim at increasing the level of evidence by validating the positive findings in prospective studies with stringent methodology.

1. Introduction

The etiology of psychiatric disorders such as bipolar disorder (BD) is largely unknown. However, the findings that drugs targeting neurotransmitters ameliorate symptoms of depression, psychosis, mania and other psychiatric symptoms support that an imbalance in the brain neurotransmitters is part of the pathophysiology. The pathophysiological processes of neurological disorders such as multiple sclerosis and Alzheimer's disease may be detectable in CSF, but for psychiatric disorders it is more difficult. Biomarkers in psychiatric disorders may assist with diagnosis, prediction of disorder course, or identification of response outcome to treatments. CSF biomarkers have been proposed in many studies but no CSF biomarkers are integrated into routine clinical practice. Although CSF biomarkers have been investigated in mania and bipolar disorder for more than half century, surprisingly, no exhaustive systematic review has ever been published on CSF biomarkers in BD.

1.1. Objectives

We aimed to systematically review studies of CSF biomarkers in patients with bipolar disorder (BD) versus healthy control individuals (HC). Further, we investigated the effect of age, gender, clinical state, medication, technical characteristics of tests, fasting state and, cognitive function if applicable. Finally, risk of bias was systematically assessed.

2. Experimental procedures

2.1. Protocol

A protocol describing methods for the review was prepared and approved by all authors prior to the study. The review is reported according to the PRISMA Statement.

2.2. Eligibility criteria

Eligible for review were original studies published in English reporting on levels of biological CSF markers in patients with diagnosis of BD compared to HC. Studies were excluded if: 1) the groups of patients with BD or the HC group comprised of less than ten 10 individuals, 2) biomarkers were assessed post-mortem, 3) patients had mixed diagnoses and data regarding patients with BD could not be extracted separately, or 4) the smaller study, when more than one publication reported results regarding identical parameters from the same study population.

2.3. Search

Studies were identified by conducting a literature search in MEDLINE and PubMed (January 1950 to August 2017) and EMBASE (1974 - August 2017) limits; English language and human, using the following search terms both as keywords and as text words: Cerebrospinal fluid AND bipolar disorder. In addition reference lists of relevant studies were searched by hand.

2.4. Study selection and data collection process

Study titles and abstracts identified by the initial search were screened by UK. Subsequent retrieval of full text articles or other additional information, assessment for eligibility and data extraction was performed independently by two researchers; UK and AHS. Disagreements were resolved by discussion with LVK.

The association between cognitive function in BD and various CSF markers has been sporadically investigated, but these data were not included in this review.

2.5. Data items

A data sheet was constructed and the following data was extracted: Study identification, age, gender, duration of illness, BD subtype, symptom severity, duration of current affective state, medication use, smoking, alcohol use, BMI, exercise or physical activity, biomarker concentration in CSF, measurement method, blinding of analysts, time of day and fasting state at lumbar puncture. In comparisons between BD patients and HC, baseline data for BD patients were used from longitudinal studies.

2.6. Risk of bias in individual studies

Tools for assessing quality in observational epidemiological studies has been given less attention compared to tools assessing quality in clinical trials. We evaluated five domains as put forward by Sanderson et al.: 1) Methods for selecting study participants by appropriate source population and inclusion or exclusion criteria, 2) Methods for measuring exposure and outcome variables by appropriate measurements for both exposure(s) and/or outcome(s), 3) Design-specific source of bias (excluding confounding) by appropriate methods outlined to deal with any design-specific issues such as recall bias, interviewer bias, biased loss to follow up or blinding, 4) Methods to control confounding by appropriate design and/or

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