Markers of neuroinflammation and neuronal injury in bipolar disorder: Relation to prospective clinical outcomes

Anniella Isgren, Carl Sellgren, Carl-Johan Ekman, Jessica Holmén-Larsson, Kaj Blennow, Henrik Zetterberg, Joel Jakobsson, Mikael Landén

Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy, University of Gothenburg, Gothenburg and Mölndal, Sweden

Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA

Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

A R T I C L E   I N F O

Article history:
Received 7 March 2017
Received in revised form 21 April 2017
Accepted 4 May 2017
Available online xxxx

Keywords:
Neuroinflammation
Bipolar disorder
Cerebrospinal fluid
Cytokines
Microglia
Disease progression

A B S T R A C T

Neuroimmune mechanisms have been linked to the pathophysiology of bipolar disorder based on studies of biomarkers in plasma, cerebrospinal fluid (CSF), and postmortem brain tissue. There are, however, no longitudinal studies investigating if CSF markers of neuroinflammation and neuronal injury predict clinical outcomes in patients with bipolar disorder. We have in previous studies found higher CSF concentrations of interleukin-8 (IL-8), monocyte chemoattractant protein 1 (MCP-1/CCL-2), chitinase-3-like protein 1 (CHI3L1/YKL-40), and neurofilament light chain (NF-L) in euthymic patients with bipolar disorder compared with controls. Here, we investigated the relationship of these CSF markers of neuroinflammation and neuronal injury with clinical outcomes in a prospective study.

77 patients with CSF analyzed at baseline were followed for 6–7 years. Associations of baseline biomarkers with clinical outcomes (manic/hypomanic and depressive episodes, suicide attempts, psychotic symptoms, inpatient care, GAF score change) were investigated.

Baseline MCP-1 concentrations were positively associated with manic/hypomanic episodes and inpatient care during follow-up. YKL-40 concentrations were negatively associated with manic/hypomanic episodes and with occurrence of psychotic symptoms. The prospective negative association between YKL-40 and manic/hypomanic episodes survived multiple testing correction. Concentrations of IL-8 and NF-L were not associated with clinical outcomes.

High concentrations of these selected CSF markers of neuroinflammation and neuronal injury at baseline were not consistently associated with poor clinical outcomes in this prospective study. The assessed proteins may be involved in adaptive immune processes or reflect a state of vulnerability for bipolar disorder rather than being of predictive value for disease progression.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Bipolar disorder is a mood disorder characterized by recurrent episodes of elevated (mania or hypomania), depressed, or mixed mood (Belmaker, 2004). Several lines of evidence indicate that the neuroimmune system and neuroinflammation play a role in the pathophysiology of bipolar disorder (Rosenblat et al., 2014).

Neuroinflammation is a wide concept involving central nervous system (CNS) innate immunological responses (O’Callaghan et al., 2008). Microglia, the resident innate immune cells of the CNS, are essential cellular mediators of neuroinflammation. Activated microglia produce cytokines and chemokines that impact synaptic plasticity, neurotransmitter metabolism, and neurocircuits relevant to mood regulation (McAfoose and Baune, 2009; Beumer et al., 2012; Haroon et al., 2012; Kraneveld et al., 2014). Another important cell type in the neuroimmune system is astrocytes, which are considered being regulators of neuroinflammatory processes and may promote or inhibit neuronal damage and inflammation depending on the kind of stimuli present in the inflamed brain.
milieu (Cekanaviciute and Buckwalter, 2016; Colombo and Farina, 2016).

Interestingly, cross-sectional studies have found associations of peripheral markers of neuroinflammation or neuronal injury with brain imaging findings and clinical features. Thus, a recent bipolar disorder study found that the serum concentrations of TNF-α, IL-8, IFN-γ, and IL-10 were associated with structural connectivity in cortico-limbic networks (Benedetti et al., 2016). Another study reported a possible relationship between pro-inflammatory gene expression and manic symptoms (Haarman et al., 2014).

But even though many studies have demonstrated peripheral inflammation in psychiatric disorders, this is not tantamount to neuroinflammation or microglial activation in the CNS (Bhattacharya et al., 2016). This is because the serum or plasma concentrations of cytokines and other proteins differ from the respective CSF (cerebrospinal fluid) concentrations due to the relative impermeability of the blood–CSF barrier (Maier et al., 2005; Bromander et al., 2012; Isgren et al., 2015). Thus, altered concentrations of CSF proteins might be more sensitive and specific to CNS processes than equivalent blood alterations. We have in previous studies found higher CSF concentrations of some markers of neuroinflammation, glial activation and neuronal injury in patients with bipolar disorder compared with control subjects. In one of these studies we found higher CSF concentrations of interleukin-8 (IL-8) in euthymic patients with bipolar disorder compared with controls, with a strong association to lithium- and antipsychotic treatment (Isgren et al., 2015). In a second study, we found increased CSF concentrations of two markers of monocyte and glial activation in patients with bipolar disorder: monocyte chemotactant protein 1 (MCP-1; also known as CCL-2) and chitinase-3-like protein 1 (CHI3L1; also known as YKL-40) (Jakobsson et al., 2015).

Finally, we have investigated CSF markers reflecting damages in brain cells and subcellular structures in patients with bipolar disorder compared with controls. We found higher levels of neurofilament light chain (NF-L; a marker of axonal damage) in patients, as well as a positive association to treatment with atypical antipsychotic drugs (Jakobsson et al., 2014). The implications of our previous findings are, however, not yet clear. The question remains open if neuroinflammation is associated with disease progression, since prospective studies of neuroinflammation and clinical outcomes are lacking (Barbosa et al., 2014). The aim of this study was thus to investigate if CSF markers of neuroinflammation and neuronal injury in patients with bipolar disorder predict important clinical outcomes during a 6–7 year follow-up period.

2. Methods and materials

2.1. Study population

Patients with bipolar disorder who had undergone clinical characterization and lumbar puncture at baseline, as well as completed a clinical 6–7 year follow-up were eligible for this study (N = 77). The baseline work-up procedures have been described in detail previously (Ryden et al., 2009). Patients were included in the St. Göran Bipolar Project, enrolling patients from the Northern Stockholm psychiatric clinic, Stockholm, Sweden, between October 2005 and April 2008. Inclusion criteria were age 18 years or older and meeting the DSM-IV-TR criteria for a bipolar disorder diagnosis (bipolar disorder type 1, type 2, or not otherwise specified). The Affective Disorder Evaluation (ADE) was used to establish the diagnosis. The ADE is a semi-structured interview that includes adapted versions of the mood modules of the Structured Clinical Interview for DSM-IV, and was developed for the Systematic Treatment Enhancement Program of Bipolar Disorder (STEP-BD) project (Sachs et al., 2003). Co-morbid psychiatric disorders were screened for by utilizing the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan, 1998). The ADE and M.I.N.I. interviews were conducted by board certified psychiatrists or residents in psychiatry. A best-estimate diagnostic decision (Leckman et al., 1982; Roy et al., 1997) was made by a consensus panel of experienced board-certified psychiatrists specialized in bipolar disorder treatment with access to patients records, ADE, M.I.N.I., and interviews with next of kin when possible. The Montgomery-Åsberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS) were used to assess depressive and manic symptoms at baseline. Function and symptom severity were measured using the Clinical Global Impression (CGI) rating scale, and the Global Assessment of Functioning (GAF) Scale divided into functional level (GAF-f) and symptom severity (GAF-s).

During follow-up, patients maintained contact with the bipolar outpatient unit and received usual psychiatric care managed by their respective responsible psychiatrist. Patients were scheduled for annual follow-up visits according to the routines in the Swedish national quality register of bipolar disorders (Karanti et al., 2015), where mood episodes and disease related events (suicide attempts, inpatient care) were documented and inserted into the patients’ electronic medical records. The psychiatric hospitals in the Stockholm county area use the same electronic health record system to document possible inpatient care. After 6–7 years, patients were contacted and re-scheduled for a comprehensive follow-up, during which patients were interviewed by board-certified psychiatrists. Prior to the interview, patients’ electronic medical records were accessed to gauge the number of mood episodes, hospitalizations, suicide attempts, and treatments during the follow-up. These events were then reviewed during an in-person interview with each patient, at which a modified version of the ADE was used to document disease related events and present status.

The change in GAF score during the follow-up time (ΔGAF) was calculated by subtracting GAF scores at baseline from GAF scores at follow-up. The clinical features of the population available for this follow-up study were compared with the study populations previously used for studying patient-control differences in CSF markers at baseline (Jakobsson et al., 2014, 2015; Isgren et al., 2015).

The study was approved by the Regional Ethics Committee in Stockholm and carried out in accordance with the Declaration of Helsinki. All participants gave oral and written consent to participate in the study. Patients were in a euthymic mood state when the consent was obtained.

2.2. Lumbar puncture

At baseline, CSF was obtained by lumbar puncture that occurred between 09.00 and 10.00 h following an overnight fast. Patients were in a stable euthymic mood as judged by a physician at the time of CSF sampling. A total volume of 12 ml was collected, inverted to avoid gradient effects, divided into aliquots and stored at −80 °C pending analyses. All samples in this study were thawed and refrozen once before analysis.

2.3. CSF analyses

IL-8 was analyzed with the MSD 96-well multi-array and multi-spot human cytokine assay (Human Cytokine Assay Ultra-Sensitive kit, Meso Scale Discovery). MCP-1 was measured using a commercial electrochemiluminescence enzyme-linked immunosorbant assay (ELISA; Human MCP-1 Ultra-Sensitive Kit, Meso Scale Discovery). YKL-40 was measured using a commercial colorimetric ELISA (Human chitinase-3 quantikine ELISA kit, R&D systems Inc.). NF-L was measured with a commercial ELISA assay (NFLight, UmanDiagnostis AB, Umeå, Sweden). All analyses were performed...
دریافت فوری
متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات