Göteborg, 2022

Cerebrospinal fluid studies of bipolar disorder

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i sal Arvid Carlsson, Medicinaregatan 3, Göteborg, den 6 maj, klockan 13.00.

av Anniella Isgren

Fakultetsopponent:
Professor Veerle Bergink
Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, USA

Avhandlingen baseras på följande delarbeten

I. Isgren A, Jakobsson J, Pålsson E, Ekman CJ, Johansson AG, Sellgren C, Blennow K, Zetterberg H, Landén M. Increased cerebrospinal fluid interleukin-8 in bipolar disorder patients associated with lithium and antipsychotic treatment. Brain, Behaviour, and Immunity 2015; 43: 198-204.
II. Jakobsson J, Bjerke M, Sahebi S, Isgren A, Ekman CJ, Sellgren C, Olsson B, Zetterberg H, Blennow K, Pålsson E, Landén M. Monocyte and microglial activation in patients with mood-stabilized bipolar disorder. Journal of Psychiatry and Neuroscience 2015; 40(4):250-258.
III. Isgren A, Sellgren C, Ekman CJ, Holmén-Larsson J, Blennow K, Zetterberg H, Jakobsson J, Landén M. Markers of neuroinflammation and neuronal injury in bipolar disorder: Relation to prospective clinical outcomes. Brain, Behaviour, and Immunity 2017; 65: 195-201.
IV. Isgren A, Göteson A, Holmén-Larsson J, Pelanis A, Sellgren C, Joas E, Sparding T, Zetterberg H, Smedler E, Jakobsson J, Landén M. Cerebrospinal fluid proteomic study of two bipolar disorder cohorts (submitted).
V. Göteson A, Isgren A, Jonsson L, Sparding T, Smedler E, Pelanis A, Zetterberg H, Jakobsson J, Pålsson E, Holmén-Larsson J, Landén M. Cerebrospinal fluid proteomics targeted for central nervous system processes in bipolar disorder. Molecular Psychiatry 2021; 26: 7446-7453.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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Cerebrospinal fluid studies of bipolar disorder

Anniella Isgren

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

Abstract

The pathophysiology of bipolar disorder remains to be elucidated. One approach to studying brain processes is analysis of cerebrospinal fluid (CSF). This thesis comprises five studies based on the Sankt Göran Bipolar Project (SBP), a naturalistic and longitudinal study investigating patients from different demographic and social backgrounds, regarding associations between bipolar disorder and biological and clinical factors. In the first two studies (*studies I* and *II*), we found increased CSF concentrations of the immune-related proteins interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and chitinase-3-like protein 1 (CHI3L1 or YKL-40) in patients in a bipolar disorder cohort compared with controls. In a later study (*study IV*), we could, however, not replicate these findings in an independent cohort. In *study III*, we longitudinally investigated associations between prospective clinical outcomes (from a 6–7-year follow-up) and the immune-related CSF proteins which we had found to differ between bipolar disorder patients and controls at baseline in *studies I* and *II*. We found a negative association between YKL-40 concentrations and manic/hypomanic episodes, but no other significant associations. In *studies IV* and *V*, we measured a large number of CSF proteins to explore case–control-associated proteins and their relation to clinical features in our two independent bipolar disorder cohorts. We found and replicated lower concentrations of growth hormone (GH) and testican-1, and higher concentrations of C-type lectin domain family 1 member B (CLEC1B) in patients compared with controls. Also, two other proteins were lower in patients with bipolar I disorder compared with controls: draxin and tumor necrosis factor receptor superfamily member 21 (TNFRSF21). All these proteins, except for CLEC1B, have known important functions in the brain. Due to limited effect sizes, the identified proteins cannot on their own serve as biomarkers for diagnostics or prognostics. However, they give clues to the biological processes underlying bipolar disorder. In regard to immune aberrations in CSF from patients with bipolar disorder, our findings were contradictory. This work brings to light challenges in CSF studies of bipolar disorder. The high intercorrelation between proteins, and the fact that many proteins are associated with demographic factors, emphasize the need for careful study designs and consideration of potential confounders.

Keywords: Biomarkers, bipolar disorder, cerebrospinal fluid, cytokines, etiology, inflammation, microglia, neuroimmune, pathophysiology, and proteomics.

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