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Blood–cerebrospinal fluid barrier dysfunction in patients with bipolar disorder in relation to antipsychotic treatment

Henrik Zetterberg [a,b,1], Joel Jakobsson [a,1], Mikael Redsäter [a], Ulf Andreasson [a], Erik Pålsson [a], Carl Johan Ekman [c], Carl Sellgren [d], Anette GM Johansson [c], Kaj Blennow [a], Mikael Landén [a,c,d,*]

[a] Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy, University of Gothenburg, Molndal, Sweden
[b] UCL Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom
[c] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[d] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Blood–cerebrospinal barrier (BCB) dysfunction has previously been shown in subjects with schizophrenia and depressed patients with attempted suicide. Bipolar disorder (BPD) shares clinical features with both these disorders, but it is unknown if the integrity of the BCB is altered also in BPD. To assess if BCB function in BPD we surveyed 134 mood-stabilized BPD patients and 86 healthy controls. Serum and cerebrospinal fluid (CSF) samples were collected and analyzed for albumin concentration by immunonephelometry. CSF/serum albumin ratio, an established measure of BCB function, was significantly elevated in BPD patients as compared to controls. After stratifying patients according to diagnostic subtype, BPD I patients had the highest CSF/serum albumin ratios. Moreover, BPD patients on antipsychotic treatment had higher CSF/serum albumin ratio than BPD patients on other treatments. When excluding BPD patients on antipsychotic treatment the difference in CSF/serum albumin ratio between the BPD and control groups disappeared. In conclusion, antipsychotic treatment in BPD is associated with elevated CSF/serum albumin ratio, tentatively as a sign of impaired BCB function. Whether this elevation is caused by antipsychotic treatment or is associated with a certain subtype of BPD, requiring antipsychotic treatment, remains to be determined.

1. Introduction

The blood–cerebrospinal fluid barrier (BCB) has an important role in maintaining a regulated microenvironment for reliable brain signaling (Abbott et al., 2006). Albumin is only synthesized in the liver, and consequently albumin in cerebrospinal fluid (CSF) is derived from the blood via passage across the BCB. The CSF/serum albumin ratio is a standard biomarker for BCB function (Tibbling et al., 1977; Reiber, 1994). An increase in this ratio indicates impaired BCB function due to increased cerebral capillary permeability or reduced CSF flow (Reiber and Peter, 2001). Increased CSF/serum albumin ratios are well-established finding in patients with various CNS disorders such as infections, inflammatory diseases, brain tumors, cerebrovascular disease (Blennow et al., 2010), Alzheimer's disease (Elovaara et al., 1985; Blennow et al., 1990), and vascular dementia (Wallin et al., 1990). However, impaired BCB function has also been proposed to associate with or contribute to various psychiatric disorders such as paranoid psychosis (Axelsson et al., 1982) and schizophrenia (Kirch et al., 1985; Bauer and Kornhuber, 1987). A study of 90 suicide attempters, whereof 44 were diagnosed with either depression or dysthymia, revealed that 18% displayed signs of impaired BCB function after the suicide attempt (Bayard-Burfield et al., 1996). A more recent study of 63 treatment-resistant affective and schizophrenic spectrum disorder patients revealed that as many as 29% had BCB dysfunction (Bechter et al., 2010). There is no previous study of BCB function in bipolar disorder patients.

The purpose of this study was to study the integrity of BCB function in BPD. We aimed to control for potential confounding factors such as other conditions that may affect the BCB, and to relate CSF/serum albumin ratio to BPD subtypes, measures of disease severity, and medication. To these ends, we compared

* Corresponding author at: Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, S-413 45 Gothenburg, Sweden.
E-mail address: mikael.landen@neuro.gu.se (M. Landén).
[1] Contributed equally to this work.

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CSF/serum albumin ratios in a large and well-characterized cohort of mood stabilized BPD patients with the corresponding measure in healthy controls.

2. Methods

2.1. Patients

Patients were recruited from the St. Goran bipolar project, enrolling patients from the bipolar unit at the Northern Stockholm Psychiatric Clinic, Stockholm, Sweden. The key clinical assessment instrument was a Swedish version of the Affective Disorder Evaluation (ADE), developed for the NIMH-sponsored Systematic treatment Enhancement Program of Bipolar Disorder (STEP-BD) (Sachs et al., 2003). Information was thereby collected on number of depressive, manic, and mixed episodes, as well as history of psychosis. The overall functioning of the patients was rated using the Global Assessment of Functioning (GAF) numeric scale (0–100) (Hall, 1995). The ADE interviews were conducted by board-certified psychiatrists working at the bipolar outpatient unit or by residents in psychiatry completing their psychiatric training at this unit (Ryden et al., 2009). To screen for other psychiatric diagnoses and alcohol or drug abuse the following instruments were used: the Mini International Neuropsychiatry Interview (M.I.N.I) (Sheehan et al., 1998), the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) and the Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2005). The patient data was presented at a diagnostic case conference where the final best-estimate diagnostic decision was derived from diagnostic instruments and medical records by a consensus panel of experienced board-certified psychiatrists specialized in bipolar disorder. The general inclusion criteria were age 18 years or older and that the patient met the DSM-IV criteria for any bipolar disorder, *i.e.*, type I, II, NOS (not otherwise specified), cyclothymia, or schizoaffective syndrome manic type. Exclusion criteria were inability to complete the standard clinical assessment or incapability of providing informed consent. For ethical reasons, patients continued to take their prescribed medications at the time of CSF sampling.

2.2. Controls

The age- and gender-matched healthy control group consisted of individuals randomly selected from the Swedish population registry by Statistics Sweden (SCB) who were contacted by letter. Persons who were interested in participating in the study contacted the study team that conducted a preliminary telephone screening to exclude severe mental health and neurological diagnoses as well as substance abuse. Eligible individuals were scheduled for a one-day comprehensive assessment. Of the controls who received the invitation letter, 14% contacted the research team. This is on par with other studies of similar nature according to SCB (personal communication). Of those controls who volunteered, 75 were excluded at the telephone interview mainly due to drug use ($N=16$), changed their mind ($N=14$), somatic ill-health ($N=12$), metal objects in body excluding magnetic resonance imaging (MRI) ($N=10$), bipolar disorder or schizophrenia in any first degree relative ($N=9$), current mental health diagnoses ($N=6$), pregnancy ($N=5$), and moved out of area ($N=2$). One subject had no documented reason for exclusion. Furthermore, one subject did not show up for the assessments. Control subjects underwent a psychiatric interview by experienced clinicians using M.I.N.I. (Sheehan et al., 1998) and the same battery of investigations that the patients underwent, including self-rating scales, somatic tests, blood tests, and lumbar puncture. Because the assessments of controls might reveal pathology, case conferences were held between examining clinicians, primary investigator and study coordinator to decide whether or not to include such individuals in the study. It was thus decided to allow past minor depressive disorders, isolated episodes of panic disorder, eating disorders or obsessive compulsive disorder which remitted spontaneously or with short-term psychotherapy. Substance abuse was screened for at the telephone interview by the nurse, in the psychiatric interview, by AUDIT (Saunders et al., 1993) and DUDIT (Berman et al., 2005), as well as by determining serum carbohydrate-deficient transferrin (CDT). Over consumption of alcohol as revealed by CDT or responses in self-tests indicating large consumption (>8 standard drinks per time more than 2 times per week, and/or amnesia and/or loss of control more than once per month) resulted in exclusion of these subjects from the study. Other exclusion criteria were neurological conditions other than mild migraine, untreated endocrinological disorders, pregnancy, dementia, recurrent depressive disorder, suspected severe personality disorders (based on interview and SCID-II personality assessment), a family history of schizophrenia or bipolar disorder in first-degree relatives.

2.3. Ethics

The study was approved by the Regional Ethics Committee in Stockholm and conducted in accordance with the latest Helsinki Protocol. All enrolled patients and controls consented orally and in writing to participate in the study after the nature of the procedures had been fully explained.

2.4. Magnetic resonance imaging

MRI scans were acquired at the MR Research Centre, Karolinska University Hospital, Stockholm. T1 weighted, T2 weighted, and fluid attenuation inversion recovery (FLAIR) T2-weighted scans were acquired using a 1.5T scanner (General Electric Signa Excite) and subsequently examined for clinically significant anatomical abnormalities by a senior radiologist.

2.5. CSF sampling

CSF sampling (lumbar puncture) was performed on euthymic patients and controls under standard conditions between 9.00 and 10.00 a.m. following an overnight fast. The spinal needle was inserted into the L3/L4 or L4/L5 interspace and a standardized volume of 12 mL CSF was collected in a polypropylene tube, gently inverted to avoid gradient effects, and divided into 1.0–1.6 mL aliquots in polypropylene tubes that were stored at -80 °C pending analysis.

2.6. Analysis of blood–CSF barrier function

Albumin levels in serum and CSF were measured at the Clinical Neurochemistry Laboratory in Molndal, Sweden, by immunonephelometry on a Beckman Immage Immunochemistry system (Beckman Instruments, Beckman Coulter, Brea, CA, USA) using a method accredited by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC). Experienced and board-certified laboratory technicians who were blinded to clinical information performed all measurements. Intra- and inter-assay coefficients of variation were below 10%. To assess BCB function, the ratio between albumin concentration in CSF (mg/L) and serum (g/L) was calculated.

2.7. Statistics

The statistics software packages Prism 5 (Graph Pad, La Jolla, USA) and SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Group differences and correlations were established by 2-tailed Mann–Whitney *U* test, spearman's rho coefficient, Fisher's exact test and/or multiple linear regression (age and gender as covariates). The CSF/serum albumin ratio was logarithmic transformed prior to parametric analyses. All reported p-values are two-sided and *p*-values below 0.05 were regarded significant.

3. Results

3.1. Demographics

The study population comprised 134 BPD patients and 86 healthy controls. Demographics and clinical characteristics of the study population are presented in Table 1. 114 Patients and 85 controls underwent magnetic resonance imaging (MRI) of the brain. 20 Patients and 15 controls displayed any abnormal MRI findings including white matter changes, Wilson's disease (one patient), multiple sclerosis (one control), and meningioma (one control).

3.2. Patient–control comparisons

The CSF/serum albumin ratio was measured in all patients and controls (Fig. 1). Men had higher CSF/serum albumin ratio than women (5.8 (4.4–7.7) as compared to 4.6 (3.7–5.9), median (interquartile range), $p<0.001$, Mann–Whitney *U* test) and there was a positive correlation to age ($r_s=0.33$, $p<0.001$, Spearman's rho correlation). Thus, age and gender were used as covariates in further statistical analyses. The CSF/serum albumin ratio was elevated in the BPD group as compared to the control group ($\beta=0.18$, $t=2.93$, d.f.$=1$, $p=0.004$). After excluding patients and controls displaying any abnormal MRI findings, the statistically significant difference between BPD patients and controls remained ($N=94$ patients and 70 controls, $\beta=0.17$, $t=2.41$, d.f.$=1$, $p=0.017$).