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Peripheral zinc and neopterin concentrations are associated with mood severity in bipolar disorder in a gender-specific manner

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ABSTRACT

Bipolar disorder (BD) is a recurrent, episodic mood disorder for which there are no current diagnostic, prognostic or theranostic biomarkers. Two peripheral markers of the acute phase immune response, zinc and neopterin, are consistently associated with severity of depression in literature. Given gender differences in clinical presentation of BD and in inflammatory processes, we aimed to explore the interaction between gender and immune biomarkers to predict mood severity in BD. Participants with DSM IV BD I and II were recruited through the Pennsylvania Psychiatric Institute during an acute mood episode. Healthy controls (HC) were recruited through advertisements. Participants fasted for at least 6 h when blood was drawn for biomarkers. We found that zinc concentrations were significantly lower in the BD group at baseline ($p < .05$), and there was also a significant interaction between gender and zinc ($p < .05$), associated with depression severity. Also, we found a significant interaction between gender and neopterin, associated with mania severity ($p < .05$). We found that mania severity was associated with neopterin in men, while depression severity was positively associated with zinc in women. Our report bears replication in larger samples and highlights the potential for differences in the underlying pathophysiology between men and women with BD.

1. Introduction

Bipolar disorder (BD) is a recurrent, episodic mood disorder with an estimated lifetime prevalence of 3.9% in the U.S. (Kessler et al., 2005). Mood episodes may be experienced in BD as major depressive, manic, hypomanic and mixed episodes (American Psychiatric Association, 2013). BD type I (BD-I) is defined by the lifetime experience of at least one manic episode, and BD type II (BD-II) is defined by the lifetime experience of at least one hypomanic episode and at least one depressive episode (American Psychiatric Association, 2013). Though many pharmacotherapies exist for BD, individuals living with BD still suffer with mood symptoms approximately 50% of the time (Judd et al., 2002). While BD is equally prevalent in men and women, the clinical presentation and co-morbidities can differ. Women with BD have higher rates than men of BD-II, co-morbid anxiety disorders, post-traumatic stress disorder (PTSD) and bulimia (Baldassano et al., 2005; Saunders et al., 2012). The risk for migraine and the impact of co-morbid migraine on poor mood outcome is greater in women with BD (Altshuler et al., 2010; Saunders et al., 2014). Moreover, poor sleep quality affects women with BD more than men with BD by increasing frequency and severity of mood episodes (Gruber et al., 2009, 2011; Saunders et al., 2015). This suggests that gender is an important moderator of symptomatology in BD and may point to differing underlying pathophysiology in men and women with BD.

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Zinc is an essential micronutrient and plays multiple roles in the brain, as a signaling element, as a co-factor in enzymatic reactions and as a modulator of the dopaminergic system (Frederickson et al., 2005). In human studies of major depressive disorder (MDD), peripheral zinc concentrations were shown to be significantly lower in groups of men and women with depression compared to healthy controls, and zinc concentration has been inversely correlated to severity of depression in men and women (McLoughlin and Hodge, 1990; Maes et al., 1994; Amani et al., 2010; Siwek et al., 2010). Also, studies in male rodents have shown that dietary zinc deficiency is causally related to depressive-like phenotypes, and zinc supplementation can reverse depressive-like behaviors (Szewczyk et al., 2002, 2009; Nowak et al., 2003; Cieślik et al., 2007; Młyniec and Nowak, 2012). In this way, literature has supported peripheral zinc as having an important role as a biomarker for both men and women in MDD. However, to our knowledge, no studies have directly probed gender differences in the relationship between peripheral zinc and BD.

Zinc concentration in the periphery is reduced in the presence of pro-inflammatory cytokines (Liuzzi et al., 2005). While some inflammatory markers have been found to be associated with mood states in BD and in MDD, the role of inflammation as an inciting, moderating or mediating factor in the development or persistence of mood episodes is unclear. Neopterin is a circulating signaling marker of cellular inflammation produced by activated macrophages, and has been shown to have an association with depression severity (Maes et al., 1994). Also, neopterin negatively correlates with peripheral zinc in men and women with MDD (Maes et al., 1994). Moreover, while there are clear gender differences in autoimmune disease, and gender-based differences in inflammatory activation due to sex hormones (Fish et al., 2008), the role of gender differences in inflammation in mood disorders has not been explored fully.

To address the gaps in knowledge regarding circulating biomarkers of zinc and inflammatory status, we measured the peripheral zinc and neopterin concentrations in symptomatic men and women with BD, in depressed or mixed states, and compared them to healthy control participants. We also examined the relationship between mood severity, zinc, and neopterin as a function of gender in participants with BD.

2. Methods

2.1. Participants

Participants with DSM IV BD I and II (N = 27, men = 14, women = 13; age range = 19-55y) were recruited through the Pennsylvania Psychiatric Institute (PPI) in Harrisburg, PA. Healthy control participants (HC, N = 31, men = 13, women = 18; age range = 20-58y), with no personal or family history of mood disorders, were recruited through advertisements posted in the Penn State College of Medicine and Penn State Milton S. Hershey Medical Center. Exclusion criteria included inability to consent, pregnancy, intoxication with alcohol or substances of abuse, major endocrinological or rheumatological illness, and use of non-steroidal anti-inflammatory drugs (NSAIDs). The study was approved by the institutional review board (IRB 39364EP) at Penn State Hershey College of Medicine and complied with the Declaration of Helsinki. No research was conducted until consent was obtained from each participant. If a participant was found to be unable to demonstrate adequate insight into illness, they were considered unable to consent.

2.2. Rating scales

The Mini Neuropsychiatric Interview, a DSM-IV TR-based structured interview assessment, was performed at baseline to confirm diagnosis of BD (Sheehan et al., 1998). Interviews were conducted by physicians and trained research assistants. Demographic information was collected from the individual, and clinical information including current medication use, smoking status was collected via self-report. Depressive symptoms were rated with Hamilton Depression Rating Scale 21 plus atypical items (HDRS-21 + AT: Hamilton, 1960). Manic symptoms were assessed with Young Mania Rating Scale (YMRS: Young et al., 1978). A combination of clinically significant manic and depressed symptoms defined a mixed-manic phenotype (MM). HDRS-21 + AT scores between 0 and 6 indicated no depression, scores between 7 and 17 indicated mild depression, scores between 18 and 24 indicated moderate depression, and scores over 24 indicated severe depression (Zimmerman et al., 2013). YMRS scores below 7 were considered not manic. Scores between 7 and 12 were mild, and above 12 were severe manic phenotypes (Young et al., 1978). Height and weight were measured, and body mass index (BMI) was calculated using the formula: weight (kg) divided by [height (m)] x [height (m)]. Biological samples were collected as described below.

During the study, participants received naturalistic treatment, and dietary intake was not controlled. After discharge from the hospital or partial hospital program, participants were followed each week by phone and assessed for clinical improvement. A return visit was scheduled with repeat measures of mood and a blood draw when the subject was asymptomatic, or after 3 months had elapsed (regardless of whether or not they had resolved symptoms). Due to irregular contact with some participants, the maximum number of days for follow-up was 187 (the median was 22 days and average was 52 days). Due to unstable housing situations, approximately 50% of the subjects were lost to follow-up (14 out of 27). At the return visit, height and weight were measured, medication use was recorded, and mood was assessed using the HDRS-21 + AT and YMRS.

2.3. Sample collection and biomarker analysis

Blood samples were drawn for serum in vacutainers in the morning between 7:15 and 10:30 AM for the BD group (average time was 8:24 AM), and between 8:00 AM and 2:00 PM for the HC group (average time was 9:19 AM). All participants had been fasting for at least 6 h at the time of blood draw. After centrifugation for 10 min at 654.03 *g*, the serum was extracted and stored in plastic tubes at −80 °C until used. For zinc analysis, serum samples were digested in nitric acid (1N) for at least 24 h and Zn^{2+} concentration was assessed using flame atomic absorption spectrometry (AAS) as previously described (Dempsey et al., 2012). Neopterin was measured by enzyme-linked immunosorbent assay (BRAHMS, Hennigsdorf, Germany) according to the manufacturer's instructions, with a detection limit of 2 nmol/L.

2.4. Statistical analysis

For comparison of zinc concentrations between Healthy Controls (HC) vs Bipolar Subjects (BD), and women vs. men groups, we used a two-way analysis of covariance (ANCOVA) with sex and diagnosis as predictor variables. Body Mass Index (BMI) was significantly different between the BD and HC groups ($t = 3.457$, $p = .001$) and was a covariate in the ANCOVA analysis. Multiple linear regression analyses were performed to analyze the predictive power of three main effects, zinc, neopterin and gender, on mood severity. For comparison of two time points, baseline and follow-up, zinc concentrations and mood scales, a paired *t*-test was used. Categorical variables between BD and HC groups were compared using a X^2 test. All statistical analyses were performed using SPSS version 22, IBM SPSS Statistics (IBM Corporation, Armonk, NY, USA) software. A significant effect was documented at $p < .05$.

3. Results

3.1. Demographic and clinical data

Table 1 describes the demographic, clinical and biological data from the sample. Thirty BD subjects were recruited, and 27 had samples