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Research report

Decreased serum zinc concentration during depressive episode in patients with bipolar disorder

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ABSTRACT

Objectives: Zinc may be involved in the pathophysiology and treatment of depressive disorder. However, data on this issue in bipolar disorder (BD) are limited. The aim of the study was to assess zinc concentrations in the blood serum of patients at various phases and stages of bipolar disorder.
Methods: The study included 129 patients with a diagnosis of bipolar disorder type I ($n=69$) or type II ($n=60$). Fifty-eight were in a depressive episode, 23 in a manic episode and 48 in remission. Fifty healthy volunteers made a control group. Zinc concentration was measured using flame atomic absorption spectrometry.
Results: Serum zinc level in patients diagnosed with BD type I in the depressive phase was significantly reduced as compared with mania, remission and healthy subjects. In the BD type II, serum zinc level in hypomania, depression or remission phase was not significantly different from the control group. In the whole group, lower level of zinc in depression compared to remission and control subjects was found during late stage of the illness but not in the early stage. Zinc concentration was not dependent on the severity of manic or depressive symptoms and subtype of depression but correlated positively with the number of manic/hypomanic relapses in the past year.
Limitations: Lack of prospective model, heterogeneity of pharmacological treatment, small number of subgroups presenting specified clinical features.
Conclusions: Decreased serum zinc concentration occurs in depression in BD type I and probably in depression in the late stage of BD.

1. Introduction

There is growing evidence to indicate the involvement of zinc turnover disturbances in the pathophysiology and treatment of depressive disorders (for a review see Siwek et al., 2013). Zinc deficiency is accompanied not only by neurological and somatic symptoms, but also by psychopathological symptoms that substantially coincide with depressive symptoms (Frederickson et al., 2005; Siwek et al., 2005).

In the central nervous system, zinc affects the activity of excitatory amino acid neurotransmitter systems and the related synaptic plasticity, which may be connected with a biological basis for depression (Duman, 2009; Serafini, 2012). Zinc acts as a modulator and a potent antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor, whose excessive activation and associated processes of excitotoxicity belong to the pathophysiology of mood disorders (Smart et al., 1994; Chen et al., 1997; Berger and Rebernik, 1999; Liu and Zhang, 2000; Low et al., 2000; Besser et al., 2009). The brain structures in which functional and structural changes occur in the course of depression are areas of a particularly high concentration of glutamatergic neurons sequestering zinc, and NMDA receptors located thereon are characterized by a high degree of vulnerability to inhibitory effects of zinc (Low et al., 2000; Izquierdo et al., 2008). Zinc also acts as an antagonist of a metabotropic glutamate receptor (type I and II) and enhances

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the activity of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Rassendren et al., 1990; Zirpel and Parks, 2001). In addition, it inhibits glycogen synthase kinase 3 beta (GSK-3B) (Gould and Manji, 2005). All these mechanisms are also associated with antidepressant response and mood stabilizing actions. Zinc exhibits antidepressant-like activity, as shown both in the preclinical (e.g. in the forced swimming test or the tail suspension test and in experimental models of depression, such as olfactory bulbectomy, chronic unpredictable stress or chronic mild stress; Kroczka et al., 2000, 2001; Nowak et al., 2003) and in clinical studies (Nowak et al., 2003; Siwek et al., 2009; Salari et al., 2015; see Siwek et al., 2013 and Nowak, 2015 for review).

In a controlled placebo study by Siwek et al. (2009), zinc supplementation of imipramine treatment significantly reduced depression scores and improved treatment outcomes in drug-resistant patients. The important role of zinc in the pathophysiology of depression may also be illustrated by studies reporting zinc level alterations in the brain and blood serum in experimental models of depression. There are also numerous reports confirming the decrease in zinc concentration (and even its deficiency) in the clinical course of unipolar depression, usually seen as a result of inflammation or acute-phase response occurring in depression, or as associated with oxidative stress (Szewczyk et al., 2008; Siwek et al., 2013).

So far, very little is known about changes in zinc concentration levels in bipolar disorder (Stanley and Wakwe, 2002; González-Estecha et al., 2011; Siwek et al., 2013). Specifically, there is a lack of data on potential alterations in the level of zinc in BD patients depending on the phase (mania, depression, remission) or staging of the illness. Therefore, the aim of the present study was to assess zinc concentrations in the blood serum of patients at various phases and stages of bipolar disorder compared with healthy volunteers, as well as to investigate the relationship between the levels of zinc and the various clinical features in the course of BD. The methodology involved case-control study to analyze the alterations in zinc levels depending on the phase and staging of bipolar disorder.

2. Subjects and methods

2.1. Participants

Patients fulfilling the diagnostic criteria for bipolar disorder according to DSM-IV-TR (regardless of illness phase) were enrolled in the study alongside healthy volunteers.

The most important exclusion criteria were: psychoactive substance misuse, somatic diseases or medication which could significantly interfere with zinc concentration in the serum. (For detailed inclusion and exclusion criteria see Siwek et al., 2015).

During the study period patients received medications of proven efficacy in the treatment of bipolar disorder. All pharmaceuticals were used alone or in combination therapy, adequate for specific phases and the clinical picture of the disease. Accordingly, 81 patients were treated with olanzapine or quetiapine, 46 patients were treated with valproate, 20 with lithium, 24 with lamotrigine and 5 with carbamazepine. In a depressive episode, besides the mood-stabilizing treatment, patients were receiving antidepressants (24-selective serotonin reuptake inhibitors (SSRIs), 35-serotonin-norepinephrine reuptake inhibitors (SNRIs) and 5-mirtazapine (detailed pharmacotherapy is presented by Siwek et al., 2015).

The severity of depressive symptoms was measured by the Montgomery-Asberg Depression Rating Scale – MADRS (Montgomery and Asberg, 1979) and the Hamilton Depression Rating Scale – HDRS (Hamilton, 1960). The severity of manic symptoms was measured by the Young Mania Rating Scale – YMRS (Young et al., 1978). In determining the staging of bipolar disorder we used the criteria proposed by Kapczinski et al. (2009a, 2009b). Because of the relatively small size of subgroups belonging to each of the stages of bipolar disorder, patients were divided into two groups: early stage of illness (corresponding to stage 1 or 2 according to Kapczinski) and late stage of illness (corresponding to stage 3 or 4 by Kapczinski).

Healthy controls were recruited from people with no past or current severe and chronic somatic or psychiatric diseases, not receiving drugs or supplements containing zinc, with no addiction to any psychoactive substances with the exclusion of caffeine and nicotine, and with no psychiatric disorders in first-degree relatives.

All participants had given informed consent to participate in the study, which was approved by the Bioethical Committee of the Jagiellonian University, Krakow.

2.2. Laboratory methods

Blood samples (max. 9.8 ml volume) were obtained from a brachial vein from each study participant, at the same time of the day (between 8 and 9 am), to avoid diurnal variation in the zinc concentration. After about 45 minutes, the blood was centrifuged at 1800 RPM for 30 min, and the serum (only non-hemolysed) was kept frozen at −80 °C until it could be analyzed. The samples were stored in zinc-free tubes for a maximum period of 4 months.

The assessment of zinc was performed in specialized laboratory of trace element analysis, Chair of Analytical Chemistry, University of Science and Technology, Cracow. The Monovette system (Sarsted, Germany) for trace element determination was used. Serum zinc levels were measured by flame atomic absorption spectrometry (FAAS) using a PerkinElmer spectrometer model 3110 (USA). The following measurements' conditions were used: air – acetylene flame, 285.2 nm wavelength, 0.7 nm slit and single-element HCL lamps. Gas flow and burner position were optimized before measurements to achieve high sensitivity. The samples were diluted appropriately to fit into the linear range of calibration curves. In the case of samples of extremely low volume (a few microliters) the additive method of sample micro-dilution was used. The lowest concentration traceability for zinc was 0.5 μg/L. Despite dilution, no sample pre-treatment procedures were applied prior to quantitative elements determination. Depending on the total sample volume, triplicate determinations were performed. The accuracy of FAAS technique was tested by means of recovery analysis, which for Zn was in the range of 94–99%. All reagents used were of analytical grade. The test tubes for Zn were thoroughly acid washed (0.1% Nitric acid) and rinsed with double distilled deionized water.

2.3. Statistics

The test $\chi 2$ was used to analyze the differences between the quality variables. Shapiro–Wilk test (with analyze of skewness and kurtosis) was performed in order to evaluate the normal distribution of quantitative data. Because of absence of normal distribution of serum zinc and age, statistical differences in case of those quantitative data were analyzed by Kruskal–Wallis one-way ANOVA on ranks or Mann–Whitney *U*-test. Correlations between quantitative variables were analyzed with the Pearson's correlation (in case of normal distribution) or Spearman rank correlation (absence of normal distribution). For testing the relationship between zinc level (as dependent variable) and selected clinical characteristics (as independent variables), we built the multiple