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Zinc and copper concentration do not differentiate bipolar disorder from major depressive disorder

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Summary

Aim. The aim of this study was to compare the zinc and copper concentration in the group of patients with bipolar disorder (BD) and major depressive disorder (MDD).

Method. 110 patients with the diagnosis of BD and 114 with MDD were qualified to the study. To assess the levels of microelements, the flame atomic absorption spectrometry (FAAS) was used in the case of zinc and the electrothermal atomic absorption spectrometry (ET AAS) was used in the case of copper.

Results. There were no differences between concentration of zinc and copper in remission and depressive phase between patients with BD and MDD. Additionally, there were also no statistically significant differences in comparisons including type I and II, early or late phase of BD and MDD.

Conclusions. The lack of differences in zinc and copper concentrations between patients with bipolar disorder and major depressive disorder might indicate that those disorders have similar etiology.

Key words: zinc, copper, affective disorders, biomarkers

Introduction

Trace elements, like zinc and copper, and their role in human organism have been examined for many decades [1, 2]. Their role is essential in many physiological processes that are necessary for life and normal development. The disturbance of concentration or metabolism of zinc and copper can lead to development of serious metabolic disturbances or disorders, including psychiatric disorders [3–7]. Many of the physiological processes that include contribution of zinc or copper are considered to be crucial in etiology of psychiatric disorders. Among those processes are, among others, neurogenesis, synaptogenesis, neuron growth, signal neurotransmission, cognitive, learning and memory processes [8, 9], functioning of the NMDA, AMPA, GABA, kainate, and glycine receptors [10], modulation of catecholamine metabolism [11, 12], antioxidant processes [11,13–15], and also participation in regulation of immune system functions [2, 11, 12, 16]. Moreover zinc and copper are structural elements of many enzymes, that participate directly or indirectly in physiological processes linked with etiology of affective disorders, especially – in enzymes involved in antioxidant processes (lysyl oxidase and superoxide dismutase) [2, 3, 17]. Detailed characteristic of zinc and copper role is beyond the scope of this article and is described in other authors' articles [18–22].

The differential diagnosis between bipolar disorder (BD) and major depressive disorder (MDD) was always a great challenge for clinicians due to the fact that both disorders might have very similar clinical picture [23, 24]. Among all psychiatric disorders BD is most commonly confused with MDD [25, 26] and according to results of one study the ratio of conversion from MDD to BD diagnosis is 33%. The change of the diagnosis occurred even many years after the onset of depressive symptoms [25]. Those results indicate that a group of patients with undiagnosed BD can receive inadequate treatment for many years and can be classified as drug-resistant patients [25]. This is one of the most important clinical problems in the treatment of affective disorders. The identification of biological markers that would differentiate BD from MDD would significantly simplify the diagnostic processes in affective disorders and enable an early start of adequate treatment [27, 28].

Aim

The aim of the present study was to compare zinc and copper concentration between group of BD and MDD patients and to assess the correlation between trace elements levels and profile of affective disorders.

Methodology

Research location

The study included patients hospitalized in the Department of Adult Psychiatry and outpatient clinic of the University Hospital in Krakow. The enrollment was preformed between 21.09.2009 and 30.07.2013r.

Recruitment

The enrollment of clinical groups of patients was done by qualified psychiatrists. The study included patients meeting diagnostic criteria for BD and MDD according to DSM-IV-TR (regardless of the stage of the illness). All participants gave their informed consent to participate in the study. The study was approved by the Jagiellonian University Bioethical Committee.

The basic exclusion criteria were as follows: lack of consent to participate in the study, diagnosis of serious mental disorder other than BD or MDD (e.g., schizophrenia, schizoaffective psychosis), disorders associated with substance abuse (excluding nicotine or caffeine addiction); co-existence of severe somatic diseases (acute and chronic); severe personality disorders; breastfeeding or pregnancy. Patients enrolled to the study were receiving drugs with proven efficacy in the treatment of BD or MDD, adequate to the its clinical picture of the illness and in accordance with current standards (monotherapy or in case of need for treatment potentialization – combined therapy).

The detailed sociodemografic and clinical characteristic as well as and inclusion and exclusion criteria (taking into account used pharmacotherapy) are included elsewhere [29, 30].

Diagnostic tools

The severity of depressive symptoms in patients was measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) [31] and the Hamilton Depression Rating Scale (HDRS) [32]. The severity of manic symptoms was measured using the Young Mania Rating Scale (YMRS) [33].

Collection, preparation and processing of blood samples. Determination of concentration of microelements in blood serum

According to the study protocol, no more than 9.8 ml of venous blood was obtained from each enrolled patient using Monovette closed blood-collection system. After the formation of the clot, the samples were centrifuged for 30 minutes at 1,800 RPM. The obtained serum was stored at – 80°C until the scheduled start of the analysis.

After thawing and mixing thoroughly, the quantitative analysis of the samples was preformed using flame atomic absorption spectrometry (FAAS) for Zn^{2+} analysis and electrothermal atomic absorption spectrometry (ET AAS) for Cu^{2+} analysis. The authors used Perkin Elmer spectrometer Model 3110 (USA), acetylene-air flame, HCL lamp, and Perkin Elmer AA spectrometer Model 3110 (USA) equipped with the Perkin Elmer HGA-600 graphite furnace. Pre-treatment temperature was 950°C and the temperature of atomization process was 2,300°C. Copper was measured at a wavelength of 324.8 nm, zinc at 213.9 nm and 0.7 nm slit. The sample measurement were preformed in triplicate. The accuracy was tested by means of recovery analysis, which for zinc was in the range of 94–99% and copper of 96–103%.

Statistical methods

The Shapiro-Wilk test was preformed in order to evaluate the normal distribution of quantitative data. Due to lack of normal distribution of quantitative data the Kruskal-Wallis univariate ANOVA or the Mann-Whitney *U* test was used.

Results

The study included a total of 224 patients; 110 patients diagnosed with BD and 114 with MDD. The detailed information about study group characteristic are included elsewhere [29, 30].

Comparison of zinc levels in depressive episodes between patients diagnosed with BD (type I and II) and MDD showed no statistically significant differences ($p = 0.50$; Mann-Whitney *U* test). For the purpose of statistical analysis the group of patients with BD type II consisted of patients with BD type II and BD not otherwise specified (BD NOS). There were also no differences in copper concentration in depressive episode between patients diagnosed with BD (BD type I and II) and MDD ($p = 0.82$; Mann-Whitney *U* test). There were no statistically significant differences in the case of the analysis of zinc levels in remission between patients with BD (BD type I and II) and MDD ($p = 0.32$; Mann-Whitney *U* test) and copper in remission in the same patient groups ($p = 0.86$; Mann-Whitney *U* test). The detailed results are shown in Table 4.

The Kruskal-Wallis ANOVA showed no statistically significant differences in zinc concentration in depressive episode in the following groups: BD type I, type II and MDD ($p = 0.17$); early and late phase of BD and MDD ($H = 1.07$; $p = 0.59$). There were also no differences in zinc levels in remission in comparison between early and late phase of BD and MDD ($H = 5.24$; $p = 0.07$). When it comes to the copper concentration analysis in the depressive episode, the Kruskal-Wallis ANOVA showed no statistically significant differences between BD type I, type II and MDD ($p = 0.76$), and between early and late BD and MDD ($H = 0.80$; $p = 0.67$). The analysis of copper levels in remission also showed no statistically significant differences in the following groups: BD type I, type II and MDD ($p = 0.52$); early and late BD and MDD ($H = 0.97$; $p = 0.61$).

The detailed results of the analysis of microelements concentrations between groups: BD type I, type II and MDD are shown in Table 2 and 3. While detailed information about levels of examined microelements in individual subgroups and episodes are presented in Table 1.

Table 1. **Serum zinc and copper concentrations in depressive episode in patients diagnosed with BD and MDD**

Patients	Episodes	
	Depression	Remission
MDD		
Copper – median (lower/upper quartile)	0.83 (0.58/1.00)	0.85 (0.70/0.96)
Zinc – median (lower/upper quartile)	0.88 (0.78/1.01)	0.97 (0.77/1.09)
BD (BD type I and II)		
Copper – median (lower/upper quartile)	0.79 (0.64/1.00)	0.83 (0.66/1.00)
Zinc – median (lower/upper quartile)	0.83 (0.69/1.03)	1.01 (0.82/1.18)
BD type I		
Copper – median (lower/upper quartile)	0.84 (0.65/1.07)	0.81 (0.61/0.95)
Zinc – median (lower/upper quartile)	0.79 (0.68/0.88)	0.91 (0.80/1.08)
BD type II		
Copper – median (lower/upper quartile)	0.77 (0.60/0.96)	0.85 (0.75/1.07)
Zinc – median (lower/upper quartile)	0.89 (0.74/1.04)	1.16 (0.91/1.94)

Table 2. **Comparison of zinc concentrations in different phases between patients with BD type I, type II and MDD**

Zinc concentration in remission	The Kruskal–Wallis test: $H = 6.44$; $p = 0.04$ *P* values for respective comparisons are placed below.		
	BP type I	BP type II	MDD
BP type I	x	0.78	1.00
BP type II	0.78	x	1.00
MDD	1.00	1.00	x
Zinc concentration in depressive phase	The Kruskal–Wallis test: $H = 3.52$; $p = 0.17$ *P* values for respective comparisons are placed below.		
	BP type I	BP type II	MDD
BP type I	x	0.24	0.27
BP type II	0.24	x	1.00
MDD	0.27	1.00	x

Table 3. **Comparison of copper concentrations in different phases between patients with BD type I, type II and MDD**

Copper concentration in remission	The Kruskal–Wallis test: $H = 1.30$; $p = 0.52$ *P* values for respective comparisons are placed below.		
	BP type I	BP type II	MDD

table continued on the next page

BP type I	x	0.78	1.00
BP type II	0.78	x	1.00
MDD	1.00	1.00	x
Copper concentration in depressive phase	The Kruskal–Wallis test: $H = 0.55$; $p = 0.76$ P values for respective comparisons are placed below.		
	BP type I	BP type II	MDD
BP type I	x	1.00	1.00
BP type II	1.00	x	1.00
MDD	1.00	1.00	x

Table 4. **Comparison of copper and zinc concentrations between patients diagnosed with BD and MDD**

Variable:	Remission. Mann–Whitney *U* test	Depressive phase. Mann–Whitney *U* test
Zinc concentration	p = 0.32 (U = 970.5; Z = 0.99)	p = 0.5 (U = 1809.0; Z = – 0.68)
Copper concentration	p = 0.86 (U = 1033.0; Z = 0.18)	p = 0.82 (U = 1996.0; Z = – 0.22)

Discussion

The obtained results of comparison between BD and MDD patients in depressive phase and remission showed no statistically significant differences in both zinc and copper concentrations. Despite the different clinical picture and course of BD and MDD, it is considered that the cause of those affective disorders might be the same. Many researchers indicate that inflammation and oxidative and nitrosative stress might be – besides the genetic issues – the most important processes responsible for development of affective disorders [34–38]. The zinc and copper ions are essential elements in those processes [2, 3, 11, 13].

In previous papers, the authors of this article have presented no significant differences in copper levels between the following groups: BD patients *vs.* healthy volunteers, and MDD patients *vs.* healthy volunteers [20, 22], which was consistent with the data obtained by other researchers [16]. However, some of the clinical studies show that patients diagnosed with affective disorders might have higher levels of copper [5, 39].

The situation is different in the case of zinc concentrations comparison. Earlier papers published by the authors have shown that in both groups of patients, with BD type I and MDD, levels of zinc were significantly lower than those obtained in the group of healthy volunteers [19, 21]. Those results were consistent with data obtained by other researchers [11, 40–42].

Summing up the obtained results, we can indicate that zinc concentration as well as copper concentration does not differentiate BD from MDD. However, lack of dif-

ferences between those two affective disorders might be an indication of the common genesis, which needs further research.

Limitations of this study include: lack of prospective model examining the dynamics of changes in the concentration of the examined microelements in the same patients in both clinical populations, variation of pharmacological treatment in the compared study groups and the inability to estimate the impact of the above-mentioned factors on the obtained results. However, it should be noted that the study was conducted on a large group of BD and MDD patients.

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