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Serum zinc levels in acute psychiatric patients: A case series

Peter Joe[a], Mara Getz[b], Samantha Redman[c], Matthew Petrilli[d], Thorsten Manfred Kranz[e], Samoon Ahmad[a], Dolores Malaspina[c,*]

[a] New York University School of Medicine, New York, NY, USA
[b] Columbia University, New York, NY, USA
[c] Icahn Mt. Sinai Medical School, New York, NY, USA
[d] Creedmoor Psychiatric Center, Queens, New York, USA
[e] Skirball Institute of Biomolecular Medicine, Department of Cell Biology, New York University, New York, NY, USA

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ABSTRACT

Zinc dysregulation is linked to neuropsychiatric disorders and a beneficial response to zinc supplementation has been demonstrated for depression. In this case series, we examined serum zinc levels with respect to clinical factors among 20 acutely ill psychiatric cases admitted to a large urban public hospital. The results showed frank clinical zinc insufficiency in a quarter of the subjects. Group-wise analyses showed a significant association between reduced serum zinc and diagnosis of depression, and reduced serum zinc in those with aggressive, assaultive, or violent behaviors. By contrast, relatively elevated zinc levels were observed in a subset of psychotic cases on antipsychotics and mood stabilizers who had no mood symptoms. In summary, clinical zinc insufficiency was common in these acutely admitted psychiatric cases. Zinc supplementation may ameliorate symptoms in certain cases and should be considered in treatment planning. A separate patient group had elevated zinc levels, which could conceivably be pathogenic. Larger studies are needed to confirm and extend this pilot data.

1. Introduction

The human body relies heavily on the essential chemical element, zinc, to execute a myriad of biological functions. Second to calcium as the most abundant divalent cation, zinc is an ideal redox-stable metal with no oxidant properties, allowing for its ionic isotope to be a metal cofactor in over 300 biochemical reactions (McCall et al., 2000; Prasad, 1995). Found throughout much of the human body, it is highly concentrated in the limbic system, including the hippocampus, hypothalamus, and amygdala (Bhowmik et al., 2010). Zinc interacts with a wide array of organic ligands, playing a crucial role in the structure and function of many proteins including enzymes, transcription factors, hormonal receptor sites and cellular membranes (Hambidge and Krebs, 2007; Nowak, 2015). Additionally, studies have linked zinc to fundamental processes including the metabolism of DNA and RNA, signal transduction, gene expression and the regulation of apoptosis (MacDonald, 2000; Prakash et al., 2015; Truong-Tran et al., 2001). With relatively high concentrations in brain regions like the hippocampus, amygdala and the cortex, zinc has many neurological implications that span the course of a lifetime, which has been observed from brain growth at infancy to the development of neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, and Huntington's disease (Frederickson and Moncrieff, 1994; Prakash et al., 2015; Takeda et al., 2000). These neurological disorders have been observed to exhibit zinc deficiency/dysregulation, altering homeostasis and resulting in possible neurotoxicity (Frederickson and Bush, 2001; Prakash et al., 2015). Concurrently, alterations in zinc homeostasis can present themselves with psychiatric symptomatology including impaired cognition, changes in behavior, learning disabilities and depression (Kenward et al., 2007; Swardfager et al., 2013b; Szewczyk et al., 2011).

Although the relationship between zinc dysregulation and psychiatric symptomatology continues to be investigated, its exact implications remain undefined. Multiple studies have demonstrated lower serum zinc levels in depressed patients in relation to healthy controls, with a meta-analysis showing a serum zinc level that is 1.85μmol/L lower in the depressed group (Swardfager et al., 2013a; Vashum et al., 2014). A negative correlation has also been observed between serum zinc levels and severity of depressive symptoms (Maes et al., 1994; Siwek et al., 2010). As depression, like most psychiatric disorders is heterogeneous, these studies may be suggestive of a certain phenotype of depression where zinc deficiency/dysregulation may be present and

* Correspondence to: Icahn Mt. Sinai Medical School, Departments of Psychiatry, Neuroscience & Genetics, One Gustave L. Levy Place, Box 1230, New York, NY 10029, USA.
E-mail address: Dolores.malaspina@mssm.edu (D. Malaspina).

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contribute to the burden of disease. As such, it can be inferred that supplementing zinc to overcome the deficiency/dysregulation, particularly in the most acutely ill population, may result in reduction of symptomatology. Several randomized controlled trials have suggested that zinc supplementation in combination with antidepressant therapy has both a significant and successful effect on improving mood in depressed patients and healthy controls (Lai et al., 2012; Nowak et al., 2003; Ranjbar et al., 2014; Sawada and Yokoi, 2010; Siwek et al., 2009; Solati et al., 2015).

Although zinc's role in psychotic disorders has not been as rigorously investigated as in depression, there is emerging evidence supporting its role in the pathology of psychotic symptoms. Zinc in normal physiology is known to act as inhibitory ligand on the N-methyl-D-aspartate (NMDA) receptor aiding in glutamatergic transmission (Hatton and Paoletti, 2005; Takeda and Tamano, 2009). Disruption in zinc levels and/or ability to bind with the NMDA receptor may result in increased release of glutamate, which has been linked to psychotic symptomatology. Although it was believed that direct action of NMDA receptor antagonists such as phencyclidine and ketamine result in psychotic symptoms, emerging research suggests hypofunctioning NMDA receptors lead to an inability to stimulate inhibitory GABAergic interneurons to glutamatergic neurons in the prefrontal cortex. Thus, this may potentiate glutamatergic excitability in the prefrontal cortex, resulting in increased levels of intracellular calcium and activation of enzymes that damage subcellular structures (Cohen et al., 2015).

Zinc has a ubiquitous role in the biological processes of several psychiatric diagnoses and symptoms. As such, further investigation of its potential implications in identifying and treating psychiatric disorders is required. Large cross-sectional studies and prospective cohorts of healthy individuals have not shown a consistent association between serum zinc or dietary zinc and depression (Kim et al., 2017; Lehto et al., 2015; Vashum et al., 2014). However these are not the most severely affected individuals. Instead, this case series is focused on the acutely ill psychiatric population admitted to an urban public hospital. This post hoc chart review evaluated clinically useful factors that may be associated with low serum zinc levels, aiming to estimate the usefulness of zinc level assessments and zinc supplementation in severely ill cases.

2. Methods

2.1. Subjects

The subjects were 20 patients admitted to a general inpatient psychiatric unit at an urban public hospital. Any patient suspected to have possible zinc deficiency based on meeting one of the following inclusion criteria had a serum zinc level obtained due to the available literature supporting its utility: (1) current treatment with valproate; (2) alcohol or other substance use disorder; and (3) history of assault, violence, or prior incarceration. The first twenty cases after the approach was implemented were included in the study. Patient diagnoses included schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, psychosis NOS, and unspecified mood disorder in this naturalistic study. Subject information extracted from clinical records included demographics, diagnosis, history of violent behavior, substance use, medications, symptoms, and medical comorbidities.

2.2. Serum zinc measurement

Morning fasting serum zinc was obtained by atomic absorption spectroscopy. Trace-metal-free tubes and special gloves were used to avoid contamination. Zinc deficiency was assessed using lower cutoffs as defined in the International Zinc Nutrition Consultative Group (IZiNCG) guidelines, which identify individuals with serum zinc below the 2.5th percentile of the population (Brown et al., 2004). For simplicity, we applied a cutoff of 70.0 μg/dL or 10.7 μmol/L for both genders, which is a stricter cutoff than would otherwise be used for men.

2.3. Statistical analyses

Characteristics of cases with reduced zinc levels were described and mean values were compared between patients with a history of aggression and patients without, and between depressed and non-depressed patients using independent samples *t*-tests for parametric and Mann-Whitney *U* tests for non-parametric data, and Fisher's exact test. Aggression was defined as having any history of aggressive, threatening, hostile behaviors or a history of assault or other physical violence. For a subgroup analysis, only those who appeared agitated, aggressive, or violent on admission and presented imminent danger were included. Statistical analysis was performed using SPSS version 23 (IBM Corp., Armonk, NY). The effects of valproate, clozapine, other antipsychotics, and alcohol use were also analyzed using a multiple regression model, employing these variables as independent predictors of the serum zinc level.

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3. Results

The 20 subjects included 15 male and 5 female patients. The mean age among males was 39.8 ± 15.8 and among females 31.0 ± 10.3 ($p = 0.263$). There was no correlation between age and serum zinc levels (Pearson correlation $r = 0.167$, $p = 0.481$). Subjects were ethnically heterogeneous, including African Americans, Caucasian and Hispanic individuals. Data on the individuals are presented in Table 1. The normal laboratory range for serum zinc at this hospital was 56–134 μg/dL.

Patients with a lifetime history of assault, violence, aggression, or threatening behavior ($n = 10$, ID 1–4,6,10,14,18–20) had a significantly lower serum zinc level compared to those without such history (77.6 ± 14.3 μg/dL vs. 101.8 ± 32.3 μg/dL, $p = 0.044$; 11.9 ± 2.2 μmol/L vs. 15.6 ± 5.0 μmol/L), although the difference was not significant when only those who were currently agitated/aggressive ($n = 6$, ID 1,2,4,6,18,19) were compared to all others (80.7 ± 16.4 μg/dL vs. 93.6 ± 30.6 μg/dL, $p = 0.347$; 12.3 ± 2.5 vs. 14.3 ± 4.7 μmol/L). (Table 2 and 3)

The subjects with the four lowest zinc levels, described below, show a common pattern of aggression, self-harm, and substance use. Subject 1 (67 μg/dL; 10.2 μmol/L) is a 22-year-old Caucasian male diagnosed with unspecified mood disorder, anxiety, and possible autism spectrum disorder, presenting with suicidal and violent ideation in the context of grandiose delusions, with a history of violence and substance use including cannabis and LSD. Subject 6 (68 μg/dL; 10.4 μmol/L) is a 27-year-old, Caucasian, transgender female, admitted for bipolar disorder, current episode manic with psychotic features. This patient has had multiple prior hospitalizations, multiple suicide attempts, and a history of assaultive, violent behavior, with an unspecified eating disorder and alcohol and cannabis use. On admission, the patient was observed to be agitated, internally preoccupied, paranoid, and threatening, with an intense affect. Subject 8 (57 μg/dL; 8.7 μmol/L) is a 27-year-old obese non-Hispanic African American male with major depressive disorder and borderline personality disorder, multiple prior hospitalizations, presenting with auditory hallucinations and non-suicidal self-injurious behavior, reporting frequent alcohol, cannabis, and ketamine use. Subject 10 (60 μg/dL; 9.2 μmol/L) is a 55-year-old non-Hispanic African American male with major depressive disorder, cocaine and heroin use disorders, and multiple prior hospitalizations, presenting with auditory hallucinations and suicidal ideation with a distant history of incarceration for a violent crime. Medical history is significant for HIV, hepatitis C, and hypertension.

Mean serum zinc of patients with major depression (ID