Journal of Trace Elements in Medicine and Biology 51 (2019) 79–85

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Epidemiology

Comparison of serum essential trace metals between patients with schizophrenia and healthy controls

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ARTICLE INFO

Keywords:
Schizophrenia
Essential trace metals
Iron
Manganese
Nickel
Molybdenum

ABSTRACT

Preclinical and clinical studies have suggested that essential trace metals (ETMs) play an important role in the pathophysiology of brain-based disorders, including schizophrenia. This case-control study aimed to evaluate the association between ETMs and schizophrenia, and to further examine the association between ETMs and clinical characteristics in schizophrenia. One-hundred and five (n = 105) subjects who meet DSM-IV criteria for schizophrenia between the ages of 18 and 40 were recruited for the study. One hundred and six (n = 106) age- and sex-matched healthy controls (HCs) were recruited for comparison. Serum concentrations of seven ETMs [i.e. iron (Fe), zinc (Zn), copper (Cu), cobalt (Co), manganese (Mn), nickel (Ni) and molybdenum (Mo)] were evaluated using inductively coupled plasma mass spectrometry, which allows for the quantitative analysis of multiple ETMs at a single time point. Compared to HCs, serum concentrations of Mn and Mo were significantly lower in patients with schizophrenia. In contrast, serum concentrations of Fe and Ni were significantly higher in patients with schizophrenia. Additionally, correlations between specific ETMs and metabolic parameters (particularly those related to liver and renal function) were found in patients with schizophrenia, and the correlations between every two ETMs in HCs were widely interrupted. Differential levels of selected ETMs (i.e., Mn, Mo, and Ni) were identified between patients with schizophrenia and HCs following adjustment for potential confounders. The findings here should therefore be evaluated in future studies.

1. Introduction

Schizophrenia is a severe, complex, and disabling mental disorder that affects approximately 1% of the global population [1]. Schizophrenia is characterized by a set of positive, negative, and cognitive symptoms, and is associated with significant morbidity and mortality [2,3]. Despite significant advancements in the understanding of the epidemiology, neurobiology, and genetics of schizophrenia, the causal mechanisms underlying the development of schizophrenia remain unknown [4]. Evidence from preclinical and clinical studies have implicated a role for trace elements in the pathophysiology of disparate brain-based disorders, namely schizophrenia. [5–7].

The human body requires essential trace metals (ETMs) during development and adult life to sustain disparate metabolic and physiological processes. ETMs, for example, iron (Fe), zinc (Zn), copper (Cu), cobalt (Co), manganese (Mn), nickel (Ni) and molybdenum (Mo) are required for proper immune system regulation, neurodevelopment, body growth, and cognitive function [8]. ETMs, namely Zn and Mn

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https://doi.org/10.1016/j.jtemb.2018.10.009
Received 15 August 2018; Received in revised form 17 September 2018; Accepted 4 October 2018

have also been reported to influence emotional processing by modulating aspects of neural transmission [9,10]. Replicated evidence has supported the association between schizophrenia and changes in serum ETM levels. Hitherto, the functional role of ETMs in schizophrenia are not elucidated in literature [11,12]. Some studies have reported reduced Zn concentrations in hair and plasma in subjects with schizophrenia compared to healthy controls (HCs) [13,14] whereas other studies have reported comparable Zn concentrations between individuals with and without schizophrenia [7,15]. Zn has also been associated with cognitive dysfunction (i.e., learning and memory impairments) in preclinical models [16]. Other ETMs have also been implicated in the pathophysiology of schizophrenia. For example, prepartum maternal Fe deficiency has been demonstrated to increase the risk of developing schizophrenia in offspring [17,18]. Finally, excess Mn levels in the brain- has a neurotoxic potential - has been reported to confer risk for developing schizophrenia [19]. Associations between levels of other ETMs (i.e., Co, Ni, Mo) and schizophrenia have also been reported [11,20,21].

Taken together, the mechanistic and clinical relevance of selected ETMs (i.e. Fe, Zn, Cu, Co, Mn, Ni, Mo) in schizophrenia remain obscure. Herein, we conducted a case-control study to compare serum ETM levels between adults with and without schizophrenia, and to investigate the associations between ETMs and different clinical characteristics in schizophrenia. The findings of the present study provide a more comprehensive understanding of the pathophysiology of ETMs in schizophrenia, and suggest that adjunctive ETM modulation could serve as new approaches to therapeutic interventions in patients with the disease.

2. Methods

2.1. Study population

We recruited 105 patients meeting Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)-defined criteria for schizophrenia that had not taken any antipsychotic drugs for a minimum of 1 month prior to hospitalization, and 106 age- and sex-matched HCs without any current and/or past psychiatric diagnosis. All subjects were recruited concurrently from the same district at the Weifang Mental Health Center in Shandong Province, China between November 2015 and September 2016. Subjects were excluded based on the following criteria: (1) < 18 or > 40 years old; (2) history of occupational exposure in the heavy metals industry; (3) diagnosis of diabetes, hyperlipidemia, cardiovascular disease, or any other severe medical condition; (4) presence of comorbid psychiatric conditions (e.g., substance use disorders); and (5) current or recent (i.e., within post-partum period of 12 months) pregnancy (suspected or confirmed) and/or breastfeeding.

The study protocol was reviewed and approved by the Ethics Review Committee of the Health Science Center, Peking University (IRB00001052-12065). All participants provided written and informed consent.

2.2. Serum sample preparation and metal analysis

Blood samples (approximately 5 mL) were collected from subjects between 7 A.M. and 9 A.M. following a 12-hour, overnight fast. After coagulation at room temperature for ~30 min, serum samples were isolated by centrifugation at 3000 *g* for 15 min at 4 ℃ and immediately stored at -80 ℃ until use. A direct dilution method was used for the metal preparation, i.e. 100 μL of each serum sample were transferred to a quartz tube, added 0.1 mL indium (2 ng/mL) as an internal standard element, then added 1.8 mL 1% nitric acid and mixed [22]. The concentrations of seven ETMs (i.e. Fe, Zn, Cu, Co, Mn, Ni and Mo) were analyzed in randomized order using inductively coupled plasma mass spectrometry (ICP-MS) (ELAN DRCII; PerkinElmer, USA). The main parameters of ICP-MS were as follows: nebulizer gas flow, 0.97 L/min; auxiliary gas flow, 1.86 L/min; plasma gas flow, 17.0 L/min; power of radio frequency generator, 1.15 KW; dwell time, 100 ms; mode peak, hopping; resolution, 0.7-0.9 au m. To avoid spectral interferences, Dynamic Reaction Cell (DRC) mode was used for the determination of Fe and Mn.

Mixed standard chemical substances for all seven ETMs with 7-point calibration curves were used for quantification. The preparation of standard chemical substances was the same as serum samples. Metal element measurements were based on the most abundant isotope for each element to avoid interference, and Level II (ClinChek® Serum Controls, REF 8884) of the certified reference material (CRM) was used for quality assurance. As shown in Supplemental Table 1, all measured metal concentrations were included in the range of their CRM with the recovery from 92.56% to 103.15%. The mixed standard chemical substances were also used to monitor the stability and repeatability of the actual samples (i.e. these were analyzed once for every 10 study samples).

2.3. Statistical analysis

All statistical analyses were conducted using SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA). Body Mass Index (BMI) was calculated using the formula weight (kg) divided by the square of height in meters *m* (kg/m^2). Descriptive statistics were performed, with continuous variables summarized using the mean and standard deviation (SD) or median and interquartile range (IQR), while categorical variables were summarized using frequencies and proportions. Statistical significance between groups was tested using the Chi-Squared (χ^2) test or Fisher's exact test for categorical variables and t-test, or Mann-Whitney *U* test for continuous variables. The median value of the ETM concentrations in HCs was used as the cut-off value in the dose-response analysis. Unconditional logistic regression models were used to explore the association between schizophrenia and ETMs. The variables of age, sex and BMI were included as potential covariates in the unconditional logistic regression model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using maximum likelihood methods. A partial correlation analysis on ranks (i.e., Spearman correlation) was used to calculate the correlation coefficients between ETM levels and metabolic parameters. The Benjamini-Hochberg false discovery rate (FDR) control was implemented to correct for multiple comparisons. A two-tailed P-value or FDR *q*-value of < 0.05 was used to indicate statistical significance.

3. Results

3.1. Demographic and clinical characteristics

Clinical and demographic characteristics for all subjects are shown in Table 1. Of the 105 recruited patients with schizophrenia, 24 (22.9%) were drug-naïve and experienced their first-episode of schizophrenia. The remaining 81 patients had recurrent and/or chronic schizophrenia and had not taken any antipsychotic drugs for a minimum of 1 month prior to hospitalization. The mean age was 29.3 years (SD = 5.6), 61 subjects were female (64.2%), and all subjects were of Chinese Han ethnicity. The mean BMI was 24.0 kg/m^2 (SD = 4.2) and 13 (13.3%) subjects were obese (i.e., BMI > 28). The mean age of onset for schizophrenia was 23.1 (SD = 5.6) years, and the median (IQR) duration of illness was 6.1 (2.8, 10.1) years. There was no statistical difference between cases and HCs in age (P = 0.920), sex (P = 0.367), BMI (P = 0.437), cigarette smoking status (P = 0.355), and alcohol consumption (P = 0.315).

Table 2 displays the blood biochemistry analysis results for metabolic parameters. No significant differences were found between cases and HCs on lipid metabolism and glucose metabolism parameters [i.e., fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC)] (all P > 0.05). In contrast, significant differences were found between