Pathobiocchemistry

Assessment of serum trace elements and electrolytes in children with childhood and atypical autism

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A R T I C L E   I N F O

Article history:
Received 12 July 2016
Received in revised form 2 September 2016
Accepted 28 September 2016

Keywords:
Autism spectrum disorders
Pervasive developmental disorder—not otherwise specified
Metals
Selenium

A B S T R A C T

The existing data demonstrate a significant interrelation between ASD and essential and toxic trace elements status of the organism. However, data on trace element homeostasis in particular ASD forms are insufficient. Therefore, the objective of the present study was to assess the level of trace elements and electrolytes in serum of children with childhood and atypical autism. A total of 48 children with ASD (24 with childhood and 24 with atypical autism) and age- and sex-adjusted controls were examined. Serum trace elements and electrolytes were assessed using inductively-coupled plasma mass spectrometry. The obtained data demonstrate that children with ASD unspecified are characterized by significantly lower Ni, Cr, and Se levels compared to the age- and sex-matched controls. At the same time, significantly decreased serum Ni and Se concentrations were detected in patients with childhood autism. In turn, children with atypical autism were characterized by more variable serum trace element spectrum. In particular, atypical autism is associated with lower serum Al, As, Ni, Cr, Mn, and Se levels in comparison to the control values. Moreover, Al and Mn concentration in this group was also lower than that in childhood autism patients. Generally, the obtained data demonstrate lower levels of both essential and toxic trace elements in atypical autism group, being indicative of profound alteration of trace elements metabolism. However, further detailed metabolic studies are required to reveal critical differences in metabolic pathways being responsible for difference in trace element status and clinical course of the disease.

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1. Introduction

Autistic spectrum disorders (ASD) are characterized by impaired reciprocal social interaction and restricted stereotype repetitive behavior [1]. According to DSM-IV-TR autistic spectrum disorders include autistic disorders (AD), pervasive developmental disorder—not otherwise specified (PDD-NOS), and Asperger syndrome [2], whereas in DSM-V ASD include only one category [3]. The first two pathologies in DSM-IV-TR are classified as childhood autism (F84.0) and atypical autism (F84.1) in ICD-10. According to ICD-10 atypical autism may be characterized by atypicality in age of onset (F84.1.10), in symptomatology (F84.1.11), and both age of onset and symptomatology (F84.1.12) [4]. Atypical autism is different from childhood autism by the absence of repetitive behaviors or communication deficits and the failure to fulfill all sets of diagnostic criteria [5]. A Danish population-based study demonstrated that atypical autism is nearly 3 times rarer than childhood autism [6].

The incidence of ASD has increased dramatically during the last decades. To date, approximately 1 child in 45 has diagnosed ASD in the USA [7]. Despite a complex aetiology of ASD [8], the growing body of data demonstrates the association between environmental pollution and increasing ASD rates [9]. Numerous studies have highlighted the role of environmental pollutants including heavy metals in the incidence of ASD [10]. In particular, an association

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http://dx.doi.org/10.1016/j.jtemb.2016.09.009
0946-672X/© 2016 Published by Elsevier GmbH.

Please cite this article in press as: A.V. Skalny, et al., Assessment of serum trace elements and electrolytes in children with childhood and atypical autism, J Trace Elem Med Biol (2016), http://dx.doi.org/10.1016/j.jtemb.2016.09.009
between mercury (Hg) [11], arsenic (As), lead (Pb) [12], aluminium (Al) [13], cadmium (Cd), and nickel (Ni) [14] exposure has been demonstrated.

Multiple studies have revealed increased toxic metal content in different bioindicative matrices of children with ASD [15–17]. At the same time, certain studies have obtained opposite results of decreased levels of heavy metals in samples from ASD children being associated with decreased detoxicative and excretory capacity [18,19]. In particular, it is hypothesized that toxic trace elements may sequester in brain [18]. Taking into account the role of oxidative stress in ASD pathogenesis [21] proxidoxidant effect of heavy metals [20] may significantly contribute to ASD [18].

The exiting data also demonstrate alteration of essential trace element and electrolyte status in ASD. In particular, it has been demonstrated that zinc (Zn) and magnesium (Mg) deficiency is a common finding in ASD children [22]. Moreover, certain antagonist interactions between copper (Cu) and Zn may also significantly contribute to ASD pathogenesis via modulation of metallothionein system, excitotoxicity, etc. [23].

The existing data on the role of trace element and mineral status modulation via supplementation [24] or heavy metal chelation [25] also demonstrate the significant interaction between mineral homeostasis and ASD pathogenesis.

The majority of studies demonstrating the association between ASD and trace element status use hair for chemical analysis [15–18]. The advantages of using hair for assessment of trace element status are associated with irreversible incorporation of metals into hair matrix, high mineralization of the sample, and non-invasiveness of sampling [26]. Therefore, hair may be used as a long-term indicator of metal exposure, whereas trace elements levels in serum are strictly regulated and may reflect only marked alterations of metal homeostasis [27]. Hair may also be indicative of environmental exposure of the organism to trace elements [28]. At the same time, hair trace elements content is highly variable and depends on a plenty of internal and external factors and its use as an indicator of metal body burden has certain limitations [29]. Moreover, certain recent studies demonstrated that hair trace elements content is not associated with ASD [30]. In turn, certain studies demonstrated that trace elements content in blood of persons with ASD is significantly associated with markers of disturbed porphyrin metabolism [31], transketolase activity [32], oxidative stress and energy metabolism [33], as well as ASD severity [34].

ASD is associated with complex neurometabolic disorders including altered cerebrospinal fluid composition [35]. Despite the presence of active brain–brain barrier and the related differences in chemical composition of human blood and CSF, these two liquids are closely related. In particular, it has been demonstrated that the levels of certain Se species in serum and CSF are interrelated [36]. Certain association between serum Mn content and Mn-species and CSF was also demonstrated [37]. Oppositely, only an indirect association between hair and CSF trace elements content may exist.

Despite the presence of a plenty of studies demonstrating the association between ASD and trace element status, data on trace element status in children with different ASD types are insufficient. Particularly, despite the absence of significant difference in plasma Cu and Zn concentration in children with AD, PDD-NOS, and Asperger’s syndrome, those with PDD-NOS were characterized by lower Zn/Cu ratio values [38]. Similarly, Russo and DeVito (2011) observed a significant increase in plasma Cu content without altered Zn levels in both childhood and atypical autism. At the same time, Cu and Zn levels differentially responded to Zn-B6 therapy in children with various ASD types [39]. However, data on other trace elements in particular ASD types (childhood autism, atypical autism) are insufficient.

Therefore, the objective of the present study was to assess the level of trace elements and electrolytes in serum of children with childhood and atypical autism.

2. Materials and methods

The study was performed in agreement with the ethical standards set in the 1964 Declaration of Helsinki and its later amendments. The protocol of the investigation was approved by the Local Ethics Committee. Before the study informed consent was obtained from the parents of the examined children. All clinical procedures (examination, blood sampling) were performed in the presence of parents. Diagnosis of ASD was set by a psychiatrist (Natalia V. Simashkova, MD, PhD, DSc) in the Scientific Center for Mental Health (Russian Academy of Medical Sciences, Moscow, Russia) according to the diagnostic criteria of World Health Organization, ICD-10 [4]. Childhood Autism Rating Scale (CARS) was also evaluated in children with clinical signs of ASD to confirm the diagnosis.

The inclusion criterion used in the present study was diagnosed ASD in children. The presence of other neuropsychiatric disorders in the examinees was excluded by the psychiatrist. In order to exclude side effects of various factors that are known to affect trace element status the following exclusion criteria were used: endocrine disorders, inflammatory and traumatic diseases, metal implants, the use of dietary mineral supplements or mineral-containing shampoos, and vegetarianism.

A total of 96 children (after exclusion of outliers) were enrolled in the present study. ASD group (unspecified) contained 48 children, whereas 48 age- and sex-adjusted healthy children were used as the control group. The age values in the ASD unspecified and the control group were 6.6 ± 1.4 and 6.5 ± 0.9 years, respectively.

In order to reveal the influence of the particular ASD type on serum trace elements the examined autistic children were divided into two groups according to ICD-10: childhood autism (F84.0) and atypical autism (F84.1) [3]. 24 sex- and age-adjusted children were included into each group. The general control group was divided into two smaller control groups 1 and 2 (n=24) for comparison with childhood autism (F84.0) and atypical autism (F84.1) in order to prevent the influence of different group size on the outcome of statistical analysis. Mean age values in the control, childhood, and atypical autism groups was 6.4 ± 1.0, 6.5 ± 1.1, and 6.7 ± 1.2 years, respectively. Each group consisted of 50% boys and 50% girls.

Blood samples were collected after an overnight fast from cubital vein using 9–mL "Vacuette" tubes (Greiner Bio-One International AG, Austria). The obtained whole blood was centrifuged at 1600g for 10 min to separate serum from cellular blood components. The obtained samples were used for chemical analysis.

Serum samples were diluted (1:15; v/v) with an acidified (pH = 2.0) diluent consisting (v/v) of 1% 1-Butanol (Merck KgaA, Darmstadt, Germany), 0.1% Triton X-100 (Sigma-Aldrich, Co., St. Louis, USA), and 0.07% HNO3 (Sigma-Aldrich, Co., St. Louis, USA) in distilled deionized water with a specific resistivity of 18.2 MΩ·cm. Serum trace elements concentration (μg/ml) was estimated using inductively-coupled plasma mass spectrometry at NexION 300D (PerkinElmer Inc., USA) equipped with ESI SC-2 DX4 autosampler (Elemental Scientific Inc., USA). Dynamic Reaction Cell technology was used for removal of the majority of atomic interferences without loss of sensitivity. The parameters of ICP-DRC-MS are indicated in Table 1. Analysis of every sample was performed in triplicate. Commercially available Universal Data Acquisition Standards Kits (PerkinElmer Inc., USA) were used for calibration of the analyzer by preparation of standards containing 0.5, 5, 10, and 50 ng/L of the studied trace elements. An internal standard containing 10 μg/L yttrium prepared from Yttrium (Y) Pure Single-Element
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