Asian Journal of Psychiatry 47 (2020) 101805

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

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

Blood and hair zinc levels in children with attention deficit hyperactivity disorder: A meta-analysis

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ARTICLE INFO

Keywords:
Zinc
ADHD
Children
Meta-analysis

ABSTRACT

We summarized the observational studies on the correlation between zinc and attention deficit hyperactivity disorder (ADHD) since 1986, extracted relevant data for meta-analysis to determine the relationship between zinc and ADHD. We searched PubMed, Scopus, Cochrane Library, EMBASE (included EMBASE and Medline), Web of Science and Clinical Trials.gov databases from inception to April 8, 2019. We assessed the blood zinc, hair zinc and ADHD by combined the standardized mean difference (SMD) and 95% confidence interval (CI). Statistical analysis was performed using Stata 14.0. We included 11 studies for meta-analysis. Of these, 8 studies comprising 1311 participants reported blood zinc and 3 studies comprising 206 participants reported hair zinc. The zinc levels in blood (SMD: -0.91, 95% CI: -1.88-0.07, P(SMD) < 0.068), and hair (SMD: 1.42, 95% CI: -4.49-7.33, P(SMD) = 0.638) not significantly compare ADHD with controls. Nevertheless, high heterogeneity (I^2 > 97.3%) emerged among the included studies. The subgroup analysis showed that the heterogeneity of samples > 100 group was significantly reduced. The sensitivity analysis found that the results changed significantly after excluding the only cross-sectional study. In conclusion, our meta-analysis showed that there was no statistically significant difference in blood zinc and hair zinc levels between ADHD children and adolescents compared with healthy children and adolescents.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) was defined as persistent inattention and/or hyperactivity-impulsivity (Shin et al., 2015). Its main characteristics are inattention, hyperactivity and impulsivity (Anjana et al., 2010; Huang et al., 2019; Verma et al., 2011), and the main types are divided into three types: inattention, hyperactivity and impulsivity, and the combination of the two (Hong et al., 2014). In recent years, the incidence of ADHD is 5%–10%, which is one of the most commonly neurodevelopmental diseases in children (Akinbami et al., 2011; Biederman, 2005; Lange et al., 2017; Yousef et al., 2011). ADHD will affect 5–15% of school-age children, of which 30–50% will continue into adolescence and some cases into adulthood (Barkley et al., 2002; Bener et al., 2014), leading to varying degrees of functional and interpersonal dysfunction during growth (Anjana et al., 2010). Since ADHD is one of the most common condition in childhood and has been studied from so many different perspectives, the role/significance of trace elements needs to be elaborated a little more. Medical or environmental factors may influence the diagnosis of ADHD (Naguy et al., 2019). Several studies suggest that genetic and environmental factors, such as a deficiency of trace elements, copper, iron, magnesium and zinc, may contribute to ADHD (Li et al., 2015; Naguy et al., 2019).

Studies have shown that trace elements (including zinc, copper, iron, magnesium, etc.) play important roles in the brain growth, neurotransmitter synthesis (Li et al., 2015), catabolism, cell metabolism (Konofal et al., 2004), neurotransmitter related metabolism, dopamine metabolism (Arnold et al., 2000; Pifl et al., 2009) and other processes. Zinc is a cofactor involved in the metabolism of neurotransmitters, melatonin, and prostaglandin enzymes (Arnold and DiSilvestro, 2005; Sandstead et al., 1998). The imbalance between the dopamine and norepinephrine systems may be one of the causes of ADHD (Biederman, 2005). Therefore, some studies have discussed the relationship between trace elements and ADHD. Several studies have shown that zinc content is lower in the ADHD group than in the control group (Arnold et al., 2005; Bekaroglu et al., 1996; Kiddie et al., 2010; Mahmoud et al., 2011; Oner et al., 2010; Salehi et al., 2016; Sun et al., 2015; Viktorinova et al., 2016; Villagomez and Ramtekkar, 2014; Zhou et al., 2016), and some studies have shown that the zinc supplement has a better effect on ADHD than placebo (Bilici et al., 2004). However, this result has not

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https://doi.org/10.1016/j.ajp.2019.09.023
Received 22 August 2019; Received in revised form 25 September 2019; Accepted 25 September 2019

been replicated in samples from around the world, and the clinical results are still contradictory (Ghanizadeh and Berk, 2013). Therefore, we summarized the observational studies on the correlation between zinc and ADHD since 1986, extracted relevant data for meta-analysis to determine the relationship between zinc and ADHD, and analyzed the potential sources of heterogeneity between studies.

2. Methods

We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

2.1. Search strategy

We searched PubMed, Scopus, Cochrane Library, EMBASE (including EMBASE and Medline), Web of Science and Clinical Trials.gov databases from inception to April 8, 2019. We used the combined keywords and MeSH terms of zinc and Attention Deficit Hyperactivity Disorders, and listed specific retrieval strategies of PubMed, Scopus and EMBASE databases in Supplementary Table 1 (Table S1). In addition, we scanned the list of references included in the article to make sure no other relevant articles were left out (Abd El Naby and Naguib, 2018; Arnold et al., 1990; Barlow and Sidani, 1986; Bekaroglu et al., 1996; Elbaz et al., 2017; Mahmoud et al., 2011; Tabatadze et al., 2018; Tippairote et al., 2017; Toren et al., 1996; Viktorinova et al., 2016; Yang et al., 2019; Yorbik et al., 2008; Yousef et al., 2011; Zhou et al., 2016).

2.2. Eligibility criteria and study selection

For eligible studies, studies must meet the following criteria: observational studies, including a case-control or cross-sectional study design comparing peripheral levels of zinc (including blood and hair) in children with ADHD and control. Exclusion criteria for the articles included: We excluded non-English articles or studies that included patients with not only ADHD but also other neurological disorders. We also excluded conference abstract, letters, notes, editorials, reviews or meta-analysis.

2.3. Data extraction and quality assessment

The two authors independently determined the included studies and extracted the data, and the differences were resolved by a third author. The following data were extracted from each study: surname name of first author, publication year, country, samples, age (year), sex(%boy), criteria of ADHD, blood, serum, plasma zinc, hair zinc level (mean ± SD), and study design.

We assessed the quality of case-control studies and cross-sectional studies using Newcastle-Ottawa Scale (NOS) and modified NOS. When evaluating the quality of case-control studies, a score of 0 to 4, 5 to 7 and 8 to 10 were considered low quality, moderate quality and high quality studies, respectively. The NOS scores in the revised version ranged from 0 to 6, and scores greater than 3 were classified as high-quality studies (Juni et al., 1999; Tseng et al., 2018).

2.4. Statistical analysis

Statistical analysis was performed using Stata 14.0. We assessed the blood zinc, hair zinc and ADHD by combining the standardized mean difference (SMD) and 95% confidence interval (CI). If P less than 0.05 or 95% CI does not include 0, it is considered statistically significant. Heterogeneity across studies were assessed using I^2. When $I^2 > 50\%$, it indicated high heterogeneity. So, we chose the random model to merge the data. We also performed the subgroup analysis and the sensitivity analysis to explore the sources of heterogeneity. Subgroup analyzed stratified studies according to blood (serum, plasma, blood), country (Egypt, Turkey, others), year of studies (≤ 2010, > 2010), Method (atomic absorption spectrophotometer, others), study type (case-control, cross-sectional), and samples (≤ 100, > 100). We measured publication bias by funnel plots and Egger's tests.

3. Results

3.1. Study selection and study characteristics

We screened 778 articles and 37 experiments from PubMed, EMBASE, Scopus, Web of Science, Cochrane Library and Clinical trial.gov platforms, as well as 4 other articles that were included by browsing the list of references. First, 419 duplicate articles were removed automatically and manually. Second, 212 unrelated studies, 102 reviews and meta-analyses, 27 conference abstracts, 30 letters or notes or editorials were excluded by scanning the titles and abstracts. Finally, 29 studies were retained for full reading. After further screening, 16 studies were excluded. Finally, 11 studies were included in this meta-analysis. Of these, 8 studies (Abd El Naby and Naguib, 2018; Bekaroglu et al., 1996; Elbaz et al., 2017; Mahmoud et al., 2011; Toren et al., 1996; Viktorinova et al., 2016; Yang et al., 2019; Yorbik et al., 2008), comprising 1311 participants reported blood zinc and 3 studies comprising 206 participants reported hair zinc (Arnold et al., 1990; Tabatadze et al., 2018; Tippairote et al., 2017), as shown in Fig. 1.

Table 1 shows the main characteristics of the included 11 observational studies published from 1990 to 2018 in this meta-analysis. One for the cross-sectional study (Abd El Naby and Naguib, 2018), the rest was case-control study. Among the 8 studies on the relationship between blood zinc and ADHD, 5 were serum zinc (Abd El Naby and Naguib, 2018; Bekaroglu et al., 1996; Elbaz et al., 2017; Mahmoud et al., 2011; Toren et al., 1996), 2 were plasma zinc (Viktorinova et al., 2016; Yorbik et al., 2008), and 1 was the concentration of zinc in whole blood (Yang et al., 2019). In addition, quality evaluations of the included studies are also shown in Table 1.

3.2. Overall meta-analysis

As shown in Figs. 2 and 3, the zinc levels in blood (SMD: -0.91, 95% CI: -1.88-0.07, P(SMD) < 0.068) and hair (SMD: 1.42, 95% CI: -4.49-7.33, P(SMD) = 0.638) not significantly compare ADHD with controls. However, there was high heterogeneity among the included studies ($I^2 > 97.3\%$).

3.3. The subgroup analysis and the sensitivity analysis

For blood zinc, to explore the sources of heterogeneity, stratified analysis based on blood (serum, plasma, blood), country (Egypt, Turkey, others), year of studies (≤ 2010, > 2010), Method (atomic absorption spectrophotometer, others), study type (case-control, cross-sectional), and samples (≤ 100, > 100) were performed. As summarized in Table 2, although heterogeneity reduced in the samples > 100 group, dramatic heterogeneity persisted in the other groups. For hair zinc, subgroup analysis was not performed due to few articles included.

Considering the heterogeneity of our study, we conducted a sensitivity analysis. After the data of same et al was removed, the merged result was changed (SMD: -1.61, 95% CI: -2.47–-0.75, P(SMD) < 0.001), but no significant changes were found in the rest (Fig. 4A). Further analysis revealed that the same study was a cross-sectional study, while the rest were case-control studies, which may be the main reason for the differences. The sensitivity analysis of hair zinc showed that the combined results did not change after each article was removed one by one (Fig. 4B).

3.4. Publication bias

The shape of funnel (Fig. 5) and Egger's test (P = 0.428 for blood