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Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: Higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder that affects cognitive and higher cognitive functions. Increasing prevalence of ASD and high rates of related comorbidities has caused serious health loss and placed an onerous burden on the supporting families, caregivers, and health care services. Heavy metals are among environmental factors that may contribute to ASD. However, due to inconsistencies across studies, it is still hard to explain the association between ASD and toxic metals. Therefore the objective of this study was to investigate the difference in heavy metal measures between patients with ASD and control subjects.

Methods: We included observational studies that measured levels of toxic metals (antimony, arsenic, cadmium, lead, manganese, mercury, nickel, silver, and thallium) in different specimens (whole blood, plasma, serum, red cells, hair and urine) for patients with ASD and for controls. The main electronic medical database (PubMed and Scopus) were searched from inception through October 2016.

Results: 52 studies were eligible to be included in the present systematic review, of which 48 studies were included in the meta-analyses. The hair concentrations of antimony (standardized mean difference (SMD) = 0.24; 95% confidence interval (CI): 0.03 to 0.45) and lead (SMD = 0.60; 95% confidence interval (CI): 0.17 to 1.03) in ASD patients were significantly higher than those of control subjects. ASD patients had higher erythrocyte levels of lead (SMD = 1.55, CI: 0.2 to 2.89) and mercury (SMD = 1.56, CI: 0.42 to 2.70). There were significantly higher blood lead levels in ASD patients (SMD = 0.43, CI: 0.02 to 0.85). Sensitivity analyses showed that ASD patients in developed but not in developing countries have lower hair concentrations of cadmium (SMD = −0.29, CI: −0.46 to −0.12). Also, such analyses indicated that ASD patients in developing but not in developed lands have higher hair concentrations of lead (SMD = 1.58, CI: 0.80 to 2.36) and mercury (SMD = 0.77, CI: 0.31 to 1.23). These findings were confirmed by meta-regression analyses indicating that development status of countries significantly influences the overall effect size of mean difference for hair arsenic, cadmium, lead, and mercury between patients with ASD and controls.

Conclusion: The findings help highlighting the role of toxic metals as environmental factors in the etiology of ASD, especially in developing lands. While there are environmental factors other than toxic metals that greatly contribute to the etiology of ASD in developed lands. It would be, thus, expected that classification of ASD includes etiological entities of ASD on the basis of implication of industrial pollutants (developed vs. developing ASD).

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder that tends to affect numerous cognitive and higher cognitive functions, importantly language (Mitchell et al., 2006), social skills (Joseph et al., 2002), memory functions (Bennetto et al., 1996),

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planning (Robinson et al., 2009) and flexibility abilities (Sinzig et al., 2008). According to the most recent statistics provided by the Autism and Developmental Disabilities Monitoring (ADDM) network, more than 1% of children in the U.S. population (1 in 68) has an ASD and its prevalence seems to be still increasing (Baio, 2012). Notably ASD is almost always associated with psychiatric co-morbid conditions (Joshi et al., 2010), thereby resulting in serious health loss (Baxter et al., 2015). Moreover, ASD not only affect the sufferer, but can touch whole families and therefore it places an onerous burden on supporting families, caregivers (Cadman et al., 2012), and health care services (Lavelle et al., 2014). These experiences explain an increasing interest, especially in the last two decades, for understanding how and why ASD impacts on the brain health.

Research led to recognition of ASD as a heterogeneous disorder that may be caused by a combination of genetic, epigenetic, and environmental factors (Persico and Bourgeron, 2006). However, the exact etiology of ASD has remained elusive. Environmental factors that may influence prenatally the incidence and/or severity of ASD include immune abnormalities, zinc deficiency, abnormal melatonin synthesis, maternal diabetes, stress, toxins, and parental age (Grabrucker, 2013). Perinatal and/or postnatal environmental factors include stress, immune abnormalities, and toxic metals (Grabrucker, 2013). There are currently high levels of evidence that proves the association between many prenatal environmental factors and increased development of ASD (Grabrucker, 2013). However there is still a great deal of debate about the postnatal influences of environmental factors.

Toxic metals are among the probable environmental factors that may contribute, either prenatally or postnatally, to ASD. This probability seems to be increasing because of the worldwide tendency to industrialization and resulting increase in human exposure to toxic metals. There are numerous sources of toxic metals in different areas depending on the types of industrial activities. The main sources toxic metals originate from are air, soils, plants, water, and sewage sludge. As well, materials associated with original sources may be contaminated with toxic metals. Sea foods, are an excellent example of such materials. They are ordinarily contaminated with harmful values of several metals, including arsenic, cadmium, lead, and mercury (Türkmen et al., 2008; Tüzen, 2003). Further, paint and refinishing activities constitute a potential source of lead (Rabinowitz et al., 1985). While cigarette smoking (Satarug and Moore, 2004) and dental amalgams (Abraham et al., 1984) may contribute to cadmium and mercury, respectively. Toxic metals can reach hyperaccumulation thresholds and even toxic levels in any tissue (Waisberg et al., 2003; Yang et al., 2005). However subclinical and clinical toxic signs and symptoms have been reported to arise despite safe levels of lead (Seppäläinen et al., 1975). It is, thus, relevant to mention that there appears to be no “safe” level of lead, and probably other toxic metals and the higher the dose the worst the effects. Toxic metals are able to speed up the release of reactive oxygen species which are regarded as signaling molecules (Apel and Hirt, 2004) in important molecular and cellular processes such as DNA repair and lipid and protein metabolism (Ercal et al., 2001). Therefore it is well-expected that toxic metals have the enduring potential to exert serious adverse effects on most of body functions and raise the probability of developing diseases, particularly cancers, cardiovascular diseases (Agarwal et al., 2011; Houston, 2007), and neurodegenerative diseases (Rybicki et al., 1993; Matés et al., 2010). Furthermore the distribution of some toxic metals, especially mercury, is altered during infectious diseases and that their accumulation in different tissues, such as brain and liver, has been associated with more mortality from infectious diseases (Bennett et al., 2001; Ilbäck et al., 2005).

Many studies have been performed to determine the profile of toxic metals in people with ASD. However, due to inconsistencies across studies, it is still hard to explain the association between ASD and toxic metals.

1.1. Aims of the study

The present systematic review and meta-analysis study was designed to examine i) the difference in heavy metal measures (antimony, arsenic, cadmium, lead, manganese, mercury, nickel, silver, and thallium) between patients with ASD and control subjects by quantitative data synthesis of reports and ii) the impact of development status of countries on the effect size of mean difference.

2. Methods and materials

The present systematic review and meta-analysis study was prepared according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Moher et al., 2009). The PRISMA statement is a 27-item checklist which has a rational design for improving the quality of reporting systematic review and meta-analysis studies. Before the study begins, the authors (A.S. and N.R.) developed study protocol which is available on request.

2.1. Information sources and search strategy

We identified relevant studies by searching the main electronic medical database, i.e. PubMed and Scopus, through October 2016. We used the following key terms in title, abstract, or key words as follows: (Mitchell et al., 2006) species (“human” OR “subject” OR “patient” OR “people” OR “person” OR “case” OR “control” OR “individual” OR “population” OR “child” OR “kid” OR “adolescent” OR “adult”) (Joseph et al., 2002) participants (“autism” OR “autistic” OR “asperger” OR “pervasive developmental disorder” OR “pervasive developmental delay”); and (Bennetto et al., 1996) exposure (“toxic heavy metal” OR “toxic metal” OR “cadmium” OR “mercury” OR “nickel” OR “lead” OR “arsenic” OR “silver” OR “antimony” OR “thallium” OR “manganese”). To include as many relevant articles as possible in the present study, backward search was performed through which the reference lists of retrieved results were screened.

2.2. Study selection

The present systematic review and meta-analysis was depicted to identify all studies that evaluated concentrations of toxic metals in serum, plasma, whole blood, red cells, hair, nail, teeth, or in urine among patients with ASD and in control subjects without ASD. We applied no language restrictions and time limit in the search strategy and study selection. As recommended by the PRISMA guidelines and graphically illustrated in Fig. 1, the study selection is a procedure composed of four main steps: identification, screening, eligibility, and inclusion. The “identification” step aimed at acquisition of all the relevant papers is a process, including forward and backward searches and then removal of duplicate records. The “screening” step is to screen results based on title/abstract. The apparently relevant papers are examined by the authors for “eligibility”. The final step is to include articles that met eligible criteria in systematic review and in meta-analysis if applicable. In the present study, meta-analysis was performed when there were three or more comparisons regarding the title. More clearly we did not carry out quantitative synthesis when there were less than three comparisons regarding the title.

Original articles were included if they met the following criteria; 1) studies that measured toxic metals (antimony, arsenic, cadmium, lead, manganese, mercury, nickel, silver, and thallium) in the whole blood, plasma, serum, red cells, hair and urine specimens in patients with ASD and in control subjects without ASD, and 2) articles that provided sufficient data, including the total number of subjects in both patients and controls and mean and standard deviation (SD) of the heavy metal levels. We also included studies providing the enough data (for example median, the first quartile, and the third quartile, or median and range, or median and standard error) to calculate mean and SD.