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Selenium status during pregnancy: Influential factors and effects on neuropsychological development among Spanish infants

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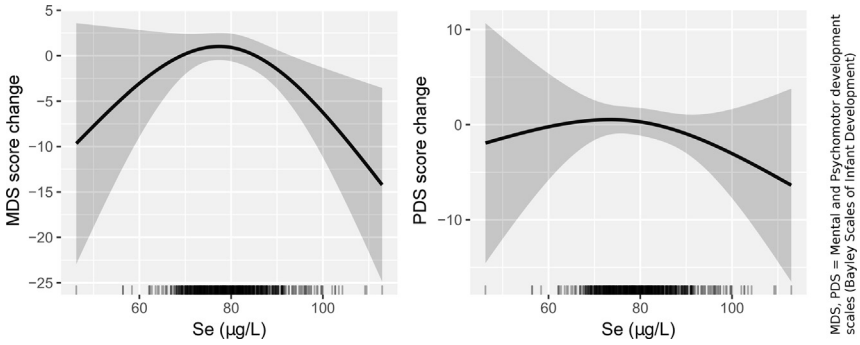
HIGHLIGHTS

- Potential neurotoxic effects of selenium at intermediate levels are scarcely studied.
- We examined the determinants of Se levels at the first trimester of gestation.
- We explored the association between maternal Se and child neurodevelopment at 12 months of age.
- An inverted U-shaped relationship was found between maternal Se and child neurodevelopment.

GRAPHICAL ABSTRACT



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ABSTRACT

Selenium (Se) has been positively associated with neurodevelopment in early life. However, its margin of safety is rather narrow, and few prospective studies have evaluated its potential neurotoxic effects at intermediate levels. We aimed to explore the association between maternal Se concentrations and child neuropsychological development, including the genetic effect modification of the Se metabolizing gene *INMT*. Study subjects were 650 mother-child pairs from the Spanish Childhood and Environment Project (INMA, 2003–2005). Infant neuropsychological development was assessed around 12 months of age by the Bayley Scales of Infant Development. Sociodemographic and dietary characteristics were collected by questionnaire at the first and third trimester of gestation. Se was measured in serum samples at the first trimester. The mean serum Se concentration was 79.7 (standard deviation = 7.9) μg/L. In multivariate analysis, nonsignificant inverse linear associations were found between Se concentrations and standardized mental and psychomotor development scores (β (95% CI) = −0.13 (−0.29, 0.03) and β (95% CI) = −0.08 (−0.24, 0.07), respectively). Generalized additive models indicated inverted U-shaped relationships between Se concentrations and both scales. Using segmented regression, the turning point for the associations was estimated at 86 μg/L for both scales. The association between Se and neuropsychological development was inverted U-shaped for children with the AG + AA genotype for rs6970396 *INMT* but a descending curve was suggested for the GG genotype. Further studies would be necessary in order to disentangle the complex equilibrium between the toxicity and benefits of Se exposure during the prenatal period.

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1. Introduction

Selenium (Se) is an essential nutrient in animals. In humans, diet is the main source of Se but the intake depends on the soil content and Se availability where the crops are grown, as well as the feed used in farm animals (Rayman, 2008). The majority of dietary Se compounds are easily absorbed in the gastrointestinal tract and then transported to the liver, where they are metabolized. Cereals, meat, fish, eggs and dairy products have been observed to be the main dietary sources of Se (McAfee et al., 2012; Rayman, 2012; Rayman et al., 2015).

Se plays a key role in several major metabolic pathways such as thyroid hormone metabolism, antioxidant defense systems and immune functions (Rayman, 2012). It is incorporated into selenoproteins in the form of selenocysteine, and is fundamental for their functioning (Bellinger et al., 2009). Of particular importance are the selenoproteins glutathione peroxidases (GPx), selenoprotein P and thioredoxin reductase, which play important roles in maintaining membrane integrity and limiting the propagation of oxidative damage to lipids, lipoproteins, and DNA (Brigelius-Flohé et al., 2003). Other essential selenoproteins are the deiodinase (DIO) proteins, which are key enzymes in thyroid hormone homeostasis (Kohrle, 2000).

Epidemiological studies conducted in populations living in high Se soil content areas have suggested that chronic exposure to high Se could lead to neurotoxicity during early development (Vinceti et al., 2014). However, very few prospective studies have evaluated the relationship between Se status during pregnancy, and child neuropsychological development among populations with intermediate Se levels, and the results obtained have been heterogeneous. Increased maternal Se concentrations were associated with better mental and psychomotor development at 1.5 years of age in Bangladesh (Skröder et al., 2015) and with better motor and language development at 1 and 2 years of age, respectively, in Poland (Polanska et al., 2016). However, in the VIVA cohort in USA, maternal blood Se was not associated with verbal or nonverbal intelligence, visual motor function or visual memory at 7.7 years of age (Oken et al., 2016). One study conducted in China observed that both low and high levels of cord serum Se were inversely associated with neurobehavioral development among newborns (Yang et al., 2013). The results derived from this last study suggested a nonlinear relationship between Se concentrations and children's neurodevelopment. This could be a possible reason for the conflicting results described above, as Se concentrations have varied markedly between studies.

Finally, it was recently found that there is a large variability in the metabolism of Se and in the urinary excretion of its metabolite trimethylselenonium ion (TMSe), and this variability was strongly linked to genetic variation of the indolethylamine *N*-methyltransferase (*INMT*) gene (Kuehnelt et al., 2015). However, it is not known whether *INMT* polymorphisms may also modify the effect of Se in children.

The aim of this study was to describe the maternal Se status in a Spanish birth cohort and to assess the influence of sociodemographic and dietary factors on it. Furthermore, we also set out to explore the relationship between maternal Se concentrations and child neuropsychological development assessed at around 12 months of age, including effect modification of an *INMT* polymorphism.

2. Methods

2.1. Population and study design

Study subjects were participants in the INMA Project (Childhood and Environment Project: http://www.proyectoinma.org) – a multicenter birth cohort study that aims to investigate the effects of environmental exposures and diet during pregnancy on fetal and child health in different areas of Spain.

The study protocol has been reported elsewhere (Guxens et al., 2012). Briefly, pregnant women were recruited at the beginning of their pregnancy in the Spanish region of Valencia ($n = 855$, 2003–2005). The inclusion criteria were: at least 16 years of age, 10–13 weeks of gestation, singleton pregnancy, intention of undergoing follow-up and delivery at the corresponding center of reference, and no impediment for communication. Excluding the women who withdrew from the study, were lost to follow-up, or had induced or spontaneous abortions or fetal deaths, a total sample of 787 (92%) women were followed up until delivery. Their children were enrolled at birth and monitored until 12 months of age ($n = 708$, 83%). The final study population was made up of 656 mothers with available serum samples to measure Se concentrations, and 651 mother–child pairs for whom Se concentrations and neuropsychological test scores were available. Genetic information was available for 349 of these children. Informed consent was obtained from all participants in each phase and the study was approved by the La Fe Hospital Ethics Committee.

2.2. Selenium concentrations

Concentrations of Se were determined in serum samples taken at the first trimester of pregnancy (mean ± standard deviation (SD) = 12.7 ± 1.5 weeks of gestation). After separation of serum through centrifugation, samples were stored at −80 °C and transported frozen to the Karolinska Institutet, Sweden, for analysis. Approximately 120 μg of serum was diluted 1:25 in an alkaline solution containing 1% NH_4OH (Merck, Darmstadt, Germany), 2% w/w 1-butanol, 0.05% EDTA, 0.05% Triton X-100 and 20 ng/g of internal standards (Sc-45, Ge-72, Rh-103; CPI International, Amsterdam, Netherlands). Samples were then sonicated and centrifuged for 5 min each. The concentrations of serum Se were determined by inductively coupled plasma mass spectrometry (ICPMS; Agilent 7700x, Agilent Technologies, Tokyo, Japan) with the collision/reaction cell system in hydrogen mode. Analytical quality control was performed by inclusion of reference materials (Seronorm™: Trace Elements serum lot MI0181, Trace Elements whole blood L-1 lot 1406263 and L-2 lot 1406264, and Medisafe serum L-2 lot 28341). The values obtained were within the analytical range or within 20% of the analytical value for all reference materials (see Supplemental Material, Table A.1). The limit of detection was 0.03 μg/L and no samples had concentrations below this value. Se concentrations were corrected according to the variations in three daily measures of the Seronorm™ (lot MI0181) reference material. The correction was performed by adding to each measure the difference between the daily mean of the reference measures and the overall mean of the reference measures.

2.3. Neuropsychological development

Neurodevelopment of the children was assessed around 12 months of age (mean ± SD = 12.3 ± 0.7, range = 11.4–19.5 months) by using the Bayley Scales of Infant Development (BSID), which assess age-appropriate mental and psychomotor development, including performance abilities, memory, early language skills, psychomotor skills and coordination. The Bayley Scales are composed of the mental scale (163 items) and the psychomotor scale (81 items). All testing was carried out at the children's reference hospital (La Fe Hospital, Valencia), in the presence of their mothers, by four trained psychologists. Raw scores were standardized for the child's age in days at test administration and for psychologist. Standardized residuals were then typified by having a mean ± SD of 100 ± 15 points to homogenize the scales.

2.4. Genetic analysis

We extracted DNA from cord blood (child genotype) as we hypothesized that the child genotype for *INMT* would be the most influential for Se concentrations in the fetus. DNA was obtained from cord blood using the Chemagen protocol (Baesweiler, Germany) at the Spanish National Genotyping Center (CEGEN). Genotyping was performed using the HumanOmni1-Quad Beadchip (Illumina, San Diego, CA, USA) at