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Relationship between the prenatal exposure to low-level of mercury and the size of a newborn's cerebellum

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ABSTRACT

Exposure to methylmercury at any stage of central nervous system development could induce alterations and result in severe congenital abnormalities. Total mercury level in maternal hair during pregnancy correlates well with blood levels of methylmercury and with total mercury levels in fetal brain.

A prospective study has been conducted and a total of 137 childbearing women living at the coastal region with term, normal pregnancies were included and their newborns evaluated by ultrasonography. Mothers and their newborns are divided in two groups according to their hair mercury levels; examined group with high body levels of mercury ($\geqslant 1$ μg/g) and control group with low body levels of mercury (<1 μg/g).

Neurosonographic examination was conducted to all newborns. Two dimensions of cerebellum in the sagital-medial plane have been measured: maximum height and width starting from the roof of the fourth chamber.

Majority of mothers had hair mercury levels lower than 1 μg/g ($N = 107$). Mean value was 0.88 μg/g (SD 1.24), ranging from 0.02 to 8.71 μg/g. There was no significant difference between the two groups when it comes to the width of cerebellum (Mann–Whitney test: $Z = 1471$; $p = 0.141$). However, comparison related to the length of cerebellum shows statistically significant smaller cerebellum in newborns whose mother had hair mercury levels higher than 1 μg/g (Mann–Whitney test: $Z = 2329$; $p = 0.019$).

Our results lead to a conclusion that prenatal exposure to, what we consider to be, low-levels of methylmercury does influence fetal brain development detected as decreased size of newborn's cerebellum.

From a clinical point of view, a question related to the influence of prenatal low-level methylmercury exposure on fetal neurodevelopment remains open. Our further objectives are to direct the research towards performing detailed neuropshychological tests on children at the age of 18 months. Such tests could indicate the presence of subtle neurological or neuropsychological deficits.

Introduction

Mercury exists in elemental, inorganic and organic form known as methylmercury [1]. In aquatic environments mercury that is leaching from the earth's crust is methylated by the action of common bacteria. Methylmercury, formed by methylation of mercury, passes up the food chain and becomes concentrated in fish and sea mammals. Consumption of seafood (fish, shelves, alga, etc.) is the primary method of exposure to methylmercury in humans [2–4].

Methylmercury passes through the placental barrier, and accumulates in the fetal organ, posing a great threat for fetus health [5,6]. Developing fetus is more vulnerable both to the exposure to methylmercury and to the effects of such exposure. The target organ for methylmercury toxicity is the brain due to its biological and metabolical immaturity and rapid growth [3,7,8].

We aimed at identifying a relationship between prenatal exposure to mercury, measured by the level of mercury in the mother's hair, and the size of a newborn cerebellum.

Hypothesis

The hypothesis was that prenatal low-level mercury exposure will have the impact on the newborns' cerebellum size.

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Methods

A prospective study has been conducted at the Department of Gynecology and Obstetrics University Hospital Rijeka, Croatia. Recruitment started in April 2007 and finished in 2008.

A total of 137 childbearing women with term pregnancies and their newborns were included in the study. Excluding criteria were: mothers suffering chronic diseases that may have a neurodevelopmental impact upon the unborn child (e.g. poorly controlled diabetes mellitus, heart disease, thyroid gland diseases, and neurological disorders), severe pregnancy complications which can influence fetal development (intrauterine growth retardation, premature delivery), proven maternal drug abuse, multiple pregnancies, language barriers (pregnant woman does not speak Croatian language), those living in the region (Primorsko-goranska county) for less than two years, inadequate hair sample (e.g. hair length insufficient for sample).

Maternal hair has been used as a vehicle for measuring prenatal exposure to mercury and the sample is taken during the first contact with pregnant women, between 27 and 32 weeks of gestation.

Collected samples have been analyzed for total mercury levels in Institute Jozef Stefan, Ljubljana, Slovenia.

Neurosonographic examination was conducted to all newborns using ALOKA SSD 4000 SV machine. In the sagital-median plane two dimensions of cerebellum have been measured: maximum height and width starting from the roof of the fourth chamber. All the measurements have been made by the same physician.

Mothers and their newborns are divided in two groups according to their hair mercury levels. Examined group consisted of newborns born to mothers with high body levels of mercury ($\geqslant 1$ μg/g). Control group consisted of newborns whose mothers had low body levels of mercury (<1 μg/g). Statistical analysis has been performed using computer program MedCalc Statistical Software (9.3.9.0, Mariakerke, Belgium). Mann–Whitney non-parametric test was used due to discrepancy in sample size and due to no normal distributions of obtained results.

Results

The average age of mothers enrolled in the study was 29, 63 (SD 4, 63). Majority of mothers had hair mercury levels lower than 1 μg/g ($N = 107$). Mean value of hair mercury level in both group was 0.88 μg/g (SD 1.24), ranging from 0.02 to 8.71 μg/g. Median values of hair mercury levels are shown in Table 1.

There was no significant difference between the two groups when it comes to the width of cerebellum, Table 2. However, comparison related to the length of cerebellum shows statistically significant smaller cerebellum in newborns whose mother had hair mercury levels higher than 1 μg/g, Table 3.

Discussion

Methylmercury poisoning in utero reveals disturbance in human fetal brain development, consisting essentially of abnormal neuronal migration, deranged cerebral cortical organization, and diffuse white matter astrocytosis with preference to phylogenetically older parts of the brain (deep subcortical nuclei, brain stem, and cerebellum) [9,10]. Exposure to methylmercury at any stage of central nervous system development could induce alterations and result in severe congenital abnormalities [11].

It is also known that severe exposures to methylmercury prenatally in Iraq were associated with morphological changes of the newborn's brain, particularly microcephaly [12]. In Mianmata, Japan, infants were born with serious neurological damage, even if their exposed mothers were virtually unaffected [13,14].

Language, attention, and memory impairment, and to a lesser extent, in visuospatial and motor functions were mostly presented mercury-related neuropsychological dysfunctions [15,16]. A case-control study revealed that an increased blood mercury level was associated with attention-deficit hyperactivity disorder [17].

Recent epidemiological studies have found more subtle adverse effects on brain functions at lower levels of methylmercury [12].

Furthermore, it has been proved that fetal growth retardation with consequential decreased birth size has unfavorable effect on neurodevelopment in childhood [18]. Results of a prospective study on a cohort of pregnant women in Spain conducted by Ramon et al. show indisputable correlation between cord blood concentration of mercury and specific anthropometric measures at birth. Higher cord blood concentrations of mercury were associated with maternal consumption of particular types of fish and reduced birth weight, birth length and an increased risk of being born small for gestational age for length. However, there was no adverse association between higher cord blood concentration of mercury and small for gestational age for weight suggesting that the role of maternal fish consumption on fetal growth depends on the amount and type of fish consumed [18].

Cranial ultrasonography is a primary method used for evaluating the neonatal brain. Structural brain abnormalities can be demonstrated and quantified by performing linear measurements of brain morphology by ultrasound [19].

We did not find data regarding prenatal low-level methylmercury exposure with the relation to its effects on the fetal brain morphology, described with neurosonographic examination.

Obtained results demonstrate that newborns born to mother with higher hair level of mercury had lower median cerebellum length, for a 1.6 mm on average, in comparison to those born to mothers with lower mercury hair level. According to our data it could be expected, with a 95% reliability (Cl 95%), that in newborns born to mothers with higher mercury hair level, cerebellum length will measure 18–20 mm, which is up to 30 mm less that the same

Table 1
Maternal hair mercury levels.

Hair mercury level μg/g			
	Mean (SD)	95% CI	Median
Examined group ($N = 30$) ($\geqslant 1$ μg/g)	2.37 (2.01)	1.62–3.12	1.67
Control group ($N = 107$) (<1 μg/g)	0.46 (0.27)	0.41–0.51	0.46

Table 2
Newborns' cerebellum widths.

Cerebellum width/mm		
	Median	95% CI
Examined group ($N = 30$)	25	24–26
Control group ($N = 107$)	26	25–26
Total ($N = 137$)	25	25–26

Mann–Whitney test: $Z = 1471$; $p = 0.141$.

Table 3
Newborns' cerebellum lengths.

Cerebellum length/mm		
	Median	95% CI
Examined group ($N = 30$)	18.4	18–20
Control group ($N = 107$)	20	20–21
Total ($N = 137$)	20	19–21

Mann–Whitney test: $Z = 2329$; $p = 0.019$.

measure in those born to mothers with lower mercury hair levels (95% CI for the median of control group was 20–21 mm).

From a clinical point of view, a question related to the influence of prenatal low-level methylmercury exposure on fetal neurodevelopment remains open. Our further objectives are to direct the research towards performing detailed neuropsychological tests on children at the age of 18 months. Such tests could indicate the presence of subtle neurological or neuropsychological deficits.

Question regarding the exact definition of 'low-level exposure' remains open, since it has not been defined as an absolute value. US Environmental Protection Agency has published recommended reference dose of 5.8 μg/l below which exposures are considered to be without adverse effect. It applies on the blood level of methylmercury in children and women [20]. To our knowledge there are no such recommendations considering the hair levels of total and methylmercury.

Majority of our sample consisted of mothers with low hair levels of mercury (<1 μg/g median 0.46 μg/g) whose newborns had greater median values of length and width of cerebellum in comparison to those with higher hair levels of mercury. Our results show that even a mean value of 2.37 μg/g i.e. the mean value of total mercury in examined group could have effect on brain development.

Total mercury levels in maternal hair have been the biological indicator of choice in nearly all previous epidemiological studies of fetal exposure to methylmercury [12]. The fact is that methylmercury accounts for over 80% of total mercury levels in hair samples [12].

Moreover, total mercury level in maternal hair during pregnancy correlates well with blood levels of methylmercury and with total mercury levels in fetal brain [12]. Bearing all mentioned above in mind, we have decided the cut off limit for low-level mercury in maternal hair to be 1 μg/g.

Our results lead to a conclusion that prenatal exposure to, what we consider to be, low-levels of methylmercury does influence fetal brain development detected as decreased size of newborn's cerebellum. Thus, further research is necessary in order to determine the exact level limit above which the total mercury level in maternal hair as well as the level of methylmercury in maternal would be considered to be toxic.

Conflicts of interest statement

None declared.

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