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Original Article

Effects of prenatal exposure to methylmercury in children auditory processing

Efeitos da exposição pré-natal ao metilmercúrio no processamento auditivo de crianças

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Abstract

Objective: to assess the central auditory processing of children exposed to mercury during the prenatal period. **Design/Study sample**: this study evaluated 90 children age eight to ten years, of both genders divided into two groups according to the levels of mercury exposure during the prenatal period: the study group (SG) was composed of children who had total Mercury levels in umbilical cord blood samples equal or higher than 8µg/L, and the control group (CG) of children who had mercury levels lower than 8µg/L. The procedures included a questionnaire, tonal threshold audiometry, word recognition audiometry, tests that assess auditory processing skills; and analysis of the total levels of mercury in umbilical cord blood samples collected at birth. **Result**: The SG presented mean total mercury in umbilical cord blood of 19.36µg/L and the CG had mean of 4.78µg/L. Regarding the tests that assess central auditory processing, the SG showed worse performance than the CG, and there was a statistically significant difference observed in the Staggered Spondaic Word Test. **Conclusion**: Children presented disorders in the tests that assess central auditory processing, indicating a possible effect of prenatal exposure to mercury in the central auditory system.

Keywords: auditory perception; mercury poisoning; child; prenatal care; public health.

Resumo

Tema: Processamento auditivo central e exposição pré-natal ao mercúrio. **Objetivo**: Avaliar processamento auditivo central de crianças expostas ao mercúrio no período pré-natal. **Método**: Foram avaliadas 90 crianças com idade de 8 a 10 anos, de ambos os sexos, categorizadas em dois grupos de acordo com os níveis de mercúrio na exposição pré-natal. O grupo de estudo (GE) foi composto por crianças que apresentaram teor de mercúrio total em amostras de sangue do cordão umbilical igual ou superior a 8 µg/L, e o grupo de controle (GC), por crianças que apresentaram teor inferior a 8 µg/L. Os procedimentos incluíram questionário, audiometria tonal liminar, logoaudiometria, testes que avaliam habilidades do processamento auditivo e análise dos teores de mercúrio total em amostras de sangue do cordão umbilical coletadas ao nascimento. **Resultado**: A média de mercúrio total no sangue do cordão umbilical do GE foi de 19,36 µg/L e o do GC, de 4,78 µg/L. Nos testes que avaliam o processamento auditivo central, o GE apresentou desempenho inferior ao GC, sendo observada diferença estatisticamente significante para o Staggered Spondaic Word Test. **Conclusão**: As crianças apresentaram alteração em testes que avaliam o processamento auditivo central, indicando um possível efeito da exposição pré-natal ao mercúrio no sistema auditivo central.

Palavras-chave: processamento auditivo; intoxicação por mercúrio; criança; pré-natal; saúde coletiva.

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INTRODUCTION

Metallic mercury, which is present in the burning of gold amalgam and methylmercury, the most toxic form, exposes the general population through the ingestion of contaminated fish, and are the main chemical forms of mercury found in the Amazon environment[1]. The use of mercury in gold mining production processes may result in serious health hazards, exposing not only the workers who are directly involved in the mines, but also the population living close to these areas, especially children[2].

Studies show that from the different population segments, children are potentially exposed to mercury since conception, through maternal exposure and transference of mercury through the placental barrier; as well as through frequent ingestion of contaminated fish throughout the years[3-5].

In a historical context, two great cases of intoxication due to the use of mercury have occurred, one in Japan in the 1950's, when several inhabitants presented a neurological disease associated to the consumption of fishes contaminated with methylmercury and became known as Minamata Disease[6,7], and in Iraq in the 1970's, where farmers and their family members, who used grains treated with fungicides made from methylmercury to make home-made bread, were contaminated[8]. In these cases, the follow-up of mothers contaminated by methylmercury, even if without signs and symptoms of intoxication, showed that they had children with adverse effects, such as low weight and muscle hypotonia, delayed neuropsychomotor development, tendency to seizures, blindness and hearing impairment. These intoxication data suggest that fetuses and children are especially at risk of developing effects of exposure to methylmercury[9].

Cohort studies were conducted following these acute intoxications in populations exposed to methylmercury through fish consumption, in the Faroe and Seychelles Islands, in both studies, the levels of mercury were measured at birth through the umbilical cord, and children were followed until adolescence. Even though these populations had lower levels of methylmercury than those in Minamata, some effects of prenatal exposure were found in these children[9]. Among the findings, disorders in brainstem auditory potential were observed which indicates methylmercury's neurotoxic effect in these children's auditory system[10].

Although the exposure to toxic levels of metals such as mercury results in adverse effects in the health of adults, this metal's toxic effects are much more devastating to the central nervous system development and general physiological system of children[11].

Regardless the form of exposure, the main effect of mercury is its neurotoxicity[9,12] and individuals exposed to this substance may suffer not only peripheral but also central damages to their auditory system. Therefore, in order to select a method for auditory evaluation of these individuals, aside from tonal and vocal audiometry, the conduction of tests which assess the entire extension of the auditory system, such as electrophysiological and central auditory tests should be considered[13].

Studies show that certain levels of exposure to heavy metals in children may affect regions of the central auditory system and describe the correlation between blood levels of mercury and disorders in central auditory processing abilities[14].

Central auditory processing (CAP) is constituted of a series of processes involved in the detection and interpretation of sound events and is characterized by a group of specific abilities, which include attention, memory, sound detection, direction, background information, among others[15,16].

The main behavioral manifestation of individuals with Central Auditory Processing Disorder is difficulty in listening and understanding in noisy environments[17], and may also present damages in attention to sound, problems in expressive language, reading and writing difficulties and behavior issues. In-depth knowledge of the problem may contribute to establishing therapy guidelines as well as to devising preventive[16].

Therefore, the present study aimed to assess the auditory processing of children exposed to mercury during the prenatal periods, and associate it to the levels of exposure to this metal.

METHODS

A cross-sectional study was conducted with children eight to ten years old of both genders, residents of the city of Itaituba, in the state of Pará, Brazil. Their performance in auditory processing tests was analyzed and correlated to mercury levels in the blood from their umbilical cords, collected at birth.

These children are part of the population of a regional vigilance program of maternal exposure to mercury in the Brazilian Amazon region, conducted by the Evandro Chagas Institute of the National Health Department since the year 2000. This program evaluated a total of 1510 mothers and their newborns which corresponded to close to 50% of all births in three hospitals of the city, during this period[5].

We conducted a search for children in the urban area of Itaituba who were followed by the program, and located a total of 93 children. The choice for children living in the urban area was made in order to reinforce the attempt of assessing the effects of prenatal exposure to mercury, since the diet of riverside children is mainly composed of fish[4]. As an inclusion criterion in this study, children should have normal inspection of the external acoustic meatus, and tonal threshold audiometry results within normal patterns. In the years of 2004, 2006 and when the auditory tests were performed, in 2010, the hair mercury levels of these children was assessed and indicated low levels of overall exposure to mercury, which means that the significant

amount of exposure occurred during the prenatal period[18]. A flow chart of the study design is shown in the Figure 1.

In order to perform a comparative analysis between prenatal exposure to mercury and auditory processing, children were divided into two groups according to levels of mercury: The study group was composed of 57 children with Hg levels in the umbilical cord blood equal to or greater than 8.0 µg/L, the control group corresponded to 33 children with Hg levels in the umbilical cord blood lower than 8.0 µg/L. This limit was based on the literature, especially on the findings published by the World Health Organization[19].

The mercury level of prenatal exposure was assessed through laboratory analysis of the total Hg levels in blood samples from the umbilical cord, collected at birth. Sample collections and analyses were performed by the Evandro Chagas Institute, following the guidelines of international quality control programs. The total mercury levels in the blood samples was determined using an atomic absorption spectrometer with cold vapor generating system (CV-AAS), type Automatic Mercury Analyzer Hg-.

Children's caregivers were informed of the objectives of the study and signed a free consent term. This study was approved by the Research Ethics Committee of the proposing institution (protocol 105/2009). After this procedure, the caregivers answered a questionnaire composed of structured, semi-structured and open questions, pertaining to speech, hearing and language development, difficulties in the reading and writing learning process, school performance and behavior characteristics of the subject, and specific questions about eating habits and exposure to mercury, which aimed to investigate possible confusion variables.

Afterwards, an inspection of the external acoustic meatus was performed, in order to verify the absence of cerumen or other elements which could interfere in auditory assessment.

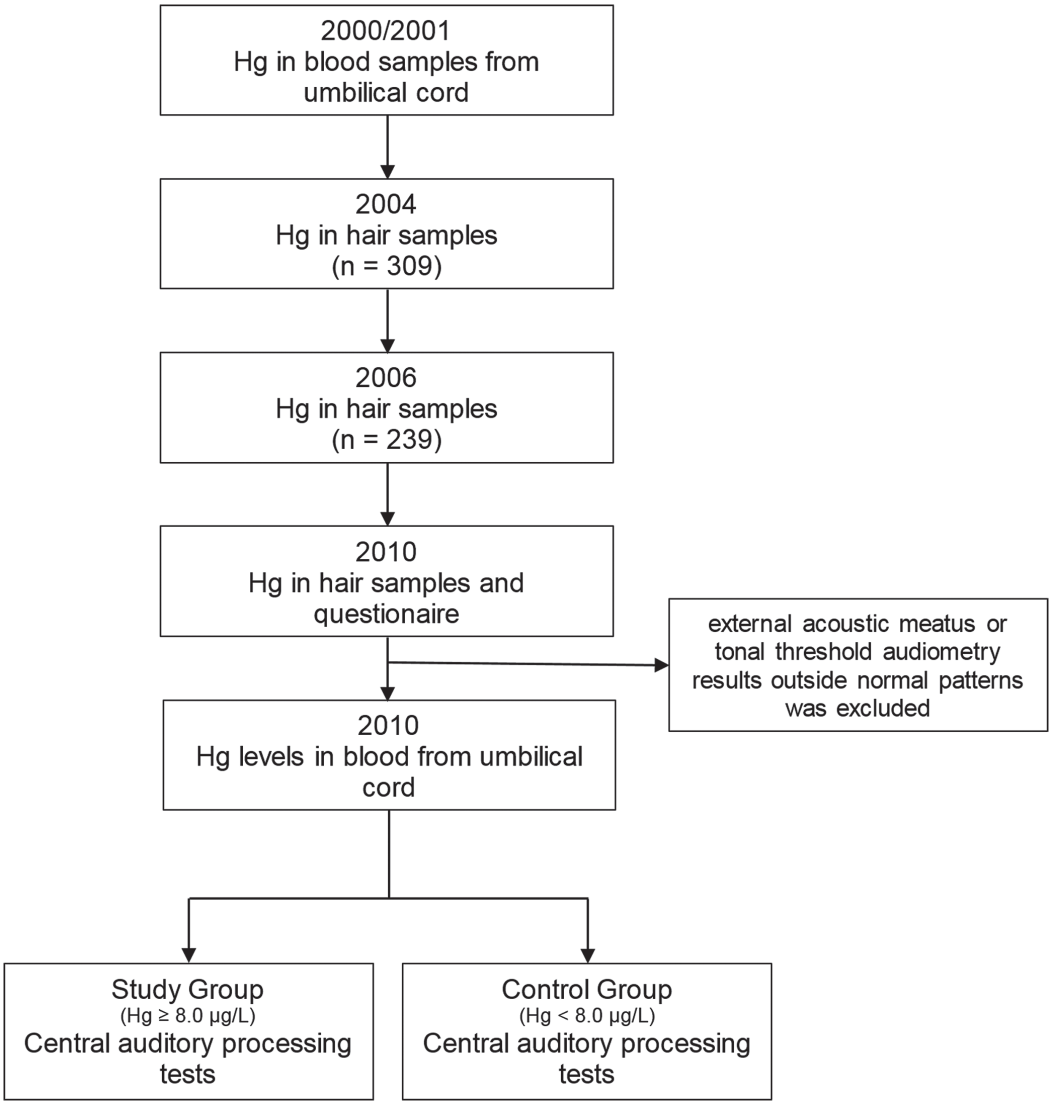

Figure 1. Study design

Children presenting alterations in this step were referred to the city's public health system and asked to return for evaluation on another date.

Auditory thresholds were assessed using an audiometer by *Interacoustic*, type AC 33, with headphones TDH - 39 and MX-41 pad. The exams were performed in a *Vibrason* brand acoustic cabin. The stimuli used for CAP assessment were the evaluator's voice, musical instruments and a Compact Disk which accompanies the handbook of central auditory processing evaluation[20].

In order to determine the minimum auditory threshold, a basic auditory assessment was performed using pure tone air conduction threshold audiometry in the frequencies of 1000Hz, 2000Hz, 3000Hz, 4000Hz, 6000Hz, 8000Hz, 250Hz e 500Hz, conducted in this order[16], where thresholds up to 25 dB were considered within normal patterns[21].

In order to have their central auditory processing assessed, children were submitted to an evaluation of their auditory skills through special behavioral tests.

The sound localization test evaluated the individual's ability to locate the sound source. The stimulus used was a rattle, played without visual aid, in five different directions in relation to the head: in front, at the back, upwards, to the left and to the right. The answer consisted of the indication of the place of sound origin and each direction was considered one correct response.

The tests which evaluated memory for verbal sounds and non-verbal sounds assessed the individual's ability to order sounds in time. To perform the memory test for verbal sound, the following segments were used in three different orders: "PA", "TA", "CA" and "FA". Initially, the child was asked to repeat each isolated segment, and then the verbal sequences were presented by the examiner. The score of correct answers in this test was determined by the number of sequences which were correctly reproduced. In order to assess memory for non-verbal sounds four sound objects were presented in three different orders. The child was asked to point to the objects in the exact order in which they were played.

The Staggered Spondaic Word Test (SSW) evaluates auditory abilities related to background figure, memory, sound-symbol association, and complex temporal order of verbal sounds. The SSW test in Portuguese uses as stimuli disyllable words in Brazilian Portuguese, which are presented at 50dBSL. In total there are 40 items composed of four words each, the first and fourth words are presented separately to each of the individual's ears, that is, without competition, and the second and third words are presented dichotically, one in each ear, simultaneously.

The SSW test result was calculated by the percentage of correct answers presented in each ear in competitive condition and the subjects were categorized in two subgroups, under 9 years old and 9 or older years old because this test presents different criteria for qualitative and quantitative responses according to age[22].

Computer software *Statistical Package for the Social Sciences* (SPSS) was used to perform the statistical analysis of the data. Descriptive statistics was used to characterize the sample's profile according to the several study variables. The t-student test was conducted in order to compare the performance in the auditory processing tests between the study and control groups. The adopted level of significance was $p < 0.05$.

RESULTS

Initially, 93 children were selected and, of these, 90 were included in the study. The three remaining children were excluded since they presented disorders of the external acoustic meatus upon evaluation.

Children in the study group (SG), composed of 57 individuals, had mean age of 8.79 years, 25 were females and 32 were males. The mean level of mercury in the umbilical cord blood was 19.36 μg/L. Children in the control group (CG), composed of 33 individuals, had mean age of 8.85 years, 17 were females and 16 were males. The mean level of mercury in the umbilical cord blood was 4.78 μg/L. All children had tonal auditory thresholds within normal patterns.

Table 1 describes individual values, means, standards deviations, minimum and maximum values and p-values in the memory test for verbal and non-verbal sounds and in the sound localization test, for each group. The mean number of correct answers in the memory for non-verbal sounds test was 2.09 in the study group and 2.30 in the control group and in the memory for verbal sounds test the mean was 1.88 for the study group and 2.21 in the control group. In the sound localization test, both groups had means greater than four correct answers.

Table 2 shows the SSW results, where the study group performance was worse than in the control group (significant difference). The mean number of correct answers in the right ear in the study group for those younger than nine years old was 70.1% and in the CG the mean was 78.4%. For those nine years old or older in the SG, the mean number of correct answers was 69.7% and for the CG it was 80.5%. In the left ear, for those younger than nine years old, the SG had a mean number of correct answers of 74.1% and the CG had a mean of 82.3% correct answers. For those nine years old or older, the SG had a mean of 73.3% of correct answers and the CG 82.3%. This difference was statistically significant for the left ear considering those younger than nine years of age (p=0.045).

DISCUSSION

Several studies highlight the importance of prenatal exposure to MeHg[1,9,23,24], since once in the human organism, it easily crosses the placental barrier, concentrating especially on the brain, and potentially inhibiting the fetus' cerebral development

Table 1. Mean, standard deviation, minimum and maximum values and p-value in the tests of verbal and non-verbal memory for sequenced sounds, and in the sound localization test for the study group (SG) and control group (CG)

Test	Group	N	Mean	Standard Deviation	Minimum	Median	Maximum	p-value[1]
SL	SG	57	4.82	0.43	3	5	5	0.693
	CG	33	4.79	0.42	4	5	5	
MSVS	SG	57	1.88	0.98	0	2	3	0.089
	CG	33	2.21	0.70	1	2	3	
MSNVS	SG	57	2.09	0.91	0	2	3	0.250
	CG	33	2.30	0.73	0	2	3	

[1] p-value (T-Student test, assuming equal variances). **SL** - Sound Localization, **MSVS** - Memory for Sequenced Verbal Sounds, **MSNVS** - Memory for Sequenced Non-Verbal Sounds

Table 2. Mean, median, standard deviation, minimum and maximum values and p-value for the SSW test for the study group (SG) and control group (CG) for children younger than 9 years of age and those 9 years or older

Test	Group	N	Mean	Standard Deviation	Minimum	Median	Maximum	p-value[1]
SSW_R	SG <9years	39	70.13	20.48	12.5	72.5	100.0	0.103
	CG <9years	22	78.41	15.13	47.5	83.8	100.0	
	SG >=9years	18	69.72	16.13	42.5	68.8	95.0	0.106
	CG >=9years	11	80.45	17.85	40.0	82.5	97.5	
SSW_L	SG <9years	39	74.10	17.90	17.5	77.5	100.0	0.045*
	CG <9years	22	82.27	13.00	57.5	86.3	100.0	
	SG >=9years	18	73.33	18.01	35.0	80.0	95.0	0.180
	CG >=9years	11	82.27	15.02	47.5	82.5	97.5	

[1] p-value (T-Student test assuming unequal variances). * Statistically significant. **SSW** - *Staggered Spondaic Word Test* in Portuguese; **SSW_R** - SSW right ear competitive; **SSW_L** - SSW left ear competitive

and thus making women in reproductive age a risk group for contamination by methylmercury. This contamination transmission may be observed in the present study, where the newborns in the SG presented mean level of mercury in their umbilical cord blood of 19.36 µg/L.

The effect of prenatal exposure to mercury in the auditory system is not yet fully explored, and most existing studies emphasize on electrophysiological tests with brainstem evoked auditory potentials as the form of evaluation of these structures. Some examples are the studies conducted by Counter[25] and Murata et al.[10]. Although these are important and bring significant data to the knowledge of the effects of mercury and other toxic substances in the auditory system, these tests do not assess the entire extension of the central auditory nervous system and do not reveal how the individual deals with the auditory information he is detecting.

Therefore, studies which use behavioral tests that evaluate the auditory system are relevant in order to increase knowledge of the adverse effects caused by exposure to mercury, mainly in the prenatal period in the auditory performance of children, and this was the main aim of the present study.

Although there is no doubt about the hazard of prenatal exposure to mercury to the health of children, safe exposure limits are still being discussed. However, important studies in this filed use the reference value suggested by the World Health Organization[19], which was then used as a cut-off point to characterize the groups as study and control. Therefore, in order to form the study and control groups based on prenatal exposure, the adopted total Hg level in the umbilical cord blood was 8.0 µg/L.

Children in the SG had mean Hg levels in their umbilical cord blood of 19.36 µg/L, and those in the CG of 4.78 µg/L (Table 1). Considering the 8.0 µg/L reference level indicated by the World Health Organization in 1990 for total Hg levels in the blood of non-exposed people, or even the 5.8 µg/L value suggested by Mahaffey et al.[26], it may be stated that the values obtained in this study's SG were high.

In the present study all children had auditory thresholds within normal patterns, considering the criteria of up to 25dBHL proposed by Silman and Silverman[21], for frequencies ranging from 250 to 8000Hz. In the comparison between the study and control groups, the means did not present significant statistical differences.

This result corroborates with those found by Murata et al.[10] in a cohort study involving 878 children exposed to methylmercury during the prenatal period, in between 7 and 14 years of age. Mercury concentration was determined by the umbilical cord and the hair of mothers and children. Tonal threshold audiometry and evoked brainstem auditory potential tests were conducted. The auditory thresholds observed in audiometry

were within normal patterns and there were disorders in the evoked brainstem auditory potentials.

Similar results were observed by Dutra et al.[27] in a study that evaluated teenagers exposed to mercury, where the auditory thresholds were within normal patterns and there were alterations in some tests which assessed auditory processing abilities, suggesting the presence of the neurotoxic effect of mercury.

In this study, the analysis of the data referring to the comparison between children in the SG and CG as far as their performance in auditory processing tests revealed similar performance among the groups in the tests for memory of verbal sequenced sounds, memory for non-verbal sequenced sounds, sound location and duration pattern tests. There were statistically significant differences between the SG and CG in the SSW test in Portuguese, where the study group had inferior performance.

In the tests that evaluate memory of verbal and non-verbal sequenced sounds, the mean values obtained by both groups, SG and CG, are in accordance to the expected correct answers classification presented by Pereira[28], which is of 2 or 3 correct answers.

In the sound localization test, the calculated descriptive means show very similar performance between both groups, and all children evaluated in this study had four or five correct answers.

Dutra et al.[27] when evaluating and comparing these same tests in adolescents with and without exposure to mercury, observed statistically significant differences in the memory for non-verbal sequenced sounds test. However, the mean results found in the tests were higher than those found in the present study in both the study and control groups.

Regarding the SSW test in Portuguese, the individuals in the SG performed worse in comparison to those in the CG, but this difference was only statistically significant for the left ears of those younger than nine years of age (p=0.045) (Table 2).

Researches with the SSW test in children show that the expected answer criteria for the right-competitive (RC) condition is 80% and left-competitive (LC) is 75% for eight-years-old children and 90% of correct answers for children aged 9 or older[22].

This data reveals that the SG had worse performance in both ears than children in the CG. Therefore, it was found that children in the SG have worse processing of verbal sounds with low levels of predictability.

This test assesses figure background skills, and similar results were found in a study which evaluated this same ability in individuals exposed to mercury[27] and solvents[29].

Although there were no studies found in literature correlating the tests that assess central auditory processing to exposure to methylmercury, studies involving other forms of mercury and other chemical agents such as solvents, lead and insecticides, found similar findings to those in the present study[27,29,30,31].

The findings in the present research as well as those in the studies mentioned above are consistent with the statement that exposure to chemical substances may affect mainly the central auditory nervous system[13].

The physiopathology of the adverse effects on health caused by chronic exposure to methylmercury on the auditory system is not yet clearly defined. However, data from studies show damage to the central nervous system among the main effects of this substance, and among the affected structures are those such as the substantia nigra, occipital and temporal lobes. This last structure has recognized relevance in auditory processing, for that is where the auditory cortex is located, which is essential for the recognizing of an organized succession of pure sounds, frequencies or different durations, as well as for the recognizing of complex sound patterns. This correlation may account for the disorders found in the present study.

Therefore, the adverse effects of prenatal exposure to methylmercury in the central nervous system may harm central auditory processing. Although studies concerning the effects of methylmercury in either peripheral or central auditory behavior are still incipient, which limits the comparison of results from the present study to others in literature, it was possible to observe effects of this substance in the central auditory system of people exposed to the impacts of gold production in Brazil.

CONCLUSION

The study group had worse performance than the control group in the assessment of the central auditory nervous system, and this difference among performances was statistically significant in the SSW test in Portuguese. These results show a possible adverse effect of mercury on children exposed during their prenatal period in the central portion of the auditory system, which is relevant in the field of public health, evaluation, prevention and follow-up measures concerning the effects of mercury in the central auditory system of this population.

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