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Brainstem auditory evoked potentials in children with low level cumulative lead exposure

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Abstract

Introduction—Earlier studies have demonstrated an auditory effect of lead exposure in children,but information on the effects of low chronic exposures needs to be further elucidated.

Objective—To investigate the effect of low chronic exposures of the auditory system in childrenwith a history of low blood lead levels, using an auditory electrophysiological test.

Methods—Contemporary cross-sectional cohort. Study participants underwent tympanometry, pure tone and speech audiometry, transient evoked otoacoustic emissions, and brainstem auditory evoked potentials, with blood lead monitoring over a period of 35.5 months. The study included 130 children, with ages ranging from 18 months to 14 years, 5 months (mean age 6years, 8 months ± 3 years, 2 months).

Results—The mean time-integrated cumulative blood lead index was 12 g/dL (SD ± 5.7, range: 2.433). All participants had hearing thresholds equal to or below 20 dBHL and normal amplitudes of transient evoked otoacoustic emissions. No association was found between the absolute latencies of waves I, III, and V, the interpeak latencies I---III, III---V, and I---V, and the cumulative lead values.

Conclusion—No evidence of toxic effects from chronic low lead exposures was observed on the auditory function of children living in a lead contaminated area.

Keywords

auditory brainstem response; pure-tone audiometry; lead contamination; ototoxicity

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Lead is a known neurotoxic agent that can cause serious damage to nervous tissue, particularly during the development of the central nervous system, causing neuro-cognitive and neurophysiological alterations in children and adults. Both occupational and environmental sources of exposure to lead are of public health concern.

Adverse health effects (mostly on cognitive function, attention and learning) have been associated with low blood lead (BPb) levels (<10-20 μg/dL or *micrograms per deciliter*) (Dietrich et al, 1992; Bellinger, 2008); Lanphear et al, 2000, 2005; Canfield et al, 2003). In a literature review on the neurotoxicity of exposure to low lead levels among children, authors concluded that there is no threshold that has no neurologic effect on the body (no-adverse effect level); that is, any exposure to lead is harmful to the central nervous system (Finkelstein et al, 1998). The US Department of Health and Human Services' (DHHS) Healthy People 2020 objectives include the elimination blood lead levels ≥ 10μg/dL among 5 year olds by the year 2020 (http://healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=12). In Brazil there is no policy directed to the prevention of intoxication by environmental exposure to heavy metals and the current Brazilian standards still consider 40 μg/dL as a recommended biological index (Brazil, 1994).

Different types of evoked potentials and numerous neurobehavioral tests have been used to detect subclinical changes in subjects exposed to a range of lead levels for the prevention of acute and/ or persistent neurological problems among the exposed (for a recent review see CDC 2012). Schwartz & Otto suggested in 1987 that evoked potential may be the most sensitive indicators of central nervous system dysfunction in children. Evidence from studies on the effects of occupational exposure to lead on the human auditory system became available in the last three decades. Latency and amplitude effects were reported through somatosensory, visual and auditory evoked potentials including cognitive evoked potentials (Seppalainen & Hernberg, 1982; Singer et al, 1983; Holdstein et al, 1986, Lille et al, 1988; Araki et al, 1992; Discalzi et al, 1992; Kovala et al, 1997; Forst et al, 1997; Farahat et al, 1997; Araki et al, 2000; Wu et al, 2000; Hwang et al, 2009; for a review see Johnson & Morata, 2010). However, there is no consensus: 1) on threshold and level of Pb intoxication necessary to induce effects on the auditory system of children, 2) on which auditory system structures or functions are susceptible, and 3) on the most sensitive tests for the evaluation of lead effects.

The first study of electrophysiological effects in lead exposed children using brainstem auditory evoked potentials was conducted by Otto et al (1985). The results showed a significant association between the original level of lead in blood (mean 28 μ/dL) and the absolute latencies of waves III and V, and an increase in latencies of these waves due to the increase in the blood lead levels. This finding suggested an effect at the level of the lower brainstem (cochlear nucleus). However, the presence of cochlear impairment was not discarded. Later studies on children with higher exposure levels (43 to72 μg/dL) also described changes in brainstem auditory evoked potentials, reinforcing the existence of auditory system impairment, but without a consensus on its sites within the auditory system. Some of these studies suggested a peripheral site of lesion (Holdstein et al, 1986, Osman et al, 1999), while others suggested both peripheral and central dysfunctions (Zou et al, 2003). However, these findings were not confirmed in later studies (Counter et al, 1997a, b) which showed no significant association between lead exposure and auditory function. With the exception of work by Holdstein et al (1986), who examined the effects of blood lead levels obtained from historical records, researchers have used measured blood lead levels at the time of investigation as a biomarker for lead exposure.

With this in perspective, the purpose of this study was to investigate the effect of chronic exposure to lead on the auditory system of children with a history of low blood lead levels, using an electrophysiological test.

Methods

This was a contemporary cross-sectional cohort study, approved by the Ethics Committee of the Institution, under No. 098/2009. Children living near a battery factory that caused lead contamination in the soil and river were recruited to participate in the study, due to their high risk of lead exposure. Those who had blood lead levels ≥10 ┐g/dL were eligible for the study, a criterion based on the 1991 recommendation of the Centers for Disease Control and Pre-vention, which identified the blood lead level of 10 ┐g/dL as ‘‘level of concern’’. The study included 130 children (80 males and 50females), aged 18 months to 14 years (mean: 6 years, 8months ± 2 years 3 months). Levels of lead in the blood were evaluated longitudinally, with all participants submitted to audiological assessment. Study participants underwent an extensive clinical evaluation by a team consisting of a pediatrician, a neurologist, a dentist, and a speech therapist, and were free of any symptoms or diagnosed disease.

Monitoring of blood lead levels in blood

The monitoring of lead levels in blood was conducted dur-ing a period lasting 35.5 months. Participants provided twoto four blood samples, collected in heparinized tubes bythe laboratory in charge following standard procedures. The analyses were performed under the control of the Municipal Health Secretariat and the city’s Regional Health Division,and were all sent to the same laboratory for analysis. Sam-ples were transported at 4°C and kept at this temperature prior to analysis. The blood lead level was obtained using atomic absorption spectrometry with graphite furnace.The data of the original sample were used to assess eligi-bility, and the eligible cases, that is, the children with bloodlead results ≥10 g/dL and without any associated disease,were followed for a period of 35.5 months. During this study,there were four sessions for blood collection; all participantswere invited to participate in each of them, but not all did.

Audiometric Screening

Initially, an otoscopic assessment was performed to exclude the presence of perforated tympanic membrane or otitis externa. The audiometric test was performed to rule out any conductive or sensorineural hearing loss in the frequencies correlated with those of the click stimulus (500---4000 Hz),with the aim of controlling interference on the results of the electrophysiological testing. The results of pure-tone audiometry were classified as normal if the hearing thresh-olds were ≤20 dBHL, obtained with a MIDIMATE 622 clinical audiometer model and TDH-39P phones. Tympanometry was performed using GSI

TympSTAR equipment, and tympanometry curves were considered normal when the static compliance was 0.3---1.3 mL and the maximum compliance peak pressure was 90---100 daPa, according to the protocol used in the service. he tests were performed in a booth with acoustic treatment in accordance with the ANSI standard.30The recording of transient evoked otoacoustic emissions(TEOAEs) was obtained in children aged 2 years, 6 months and older, using the Otodynamics ILO292 DP ECHO Research OAE System. The probe stability was always >80% and the stimulus was calibrated before each day of data collection. Criteria were the presence of TEOAE response, reproducibility of 70% or higher, and a response amplitude <3 dB in the frequency band of 1500---5000 Hz. The results of pure tone audiometry, TEOAE, and tympanometry were within normal clinical values, confirming the absence of sensorineural or conductive hearing loss in all participants.

BAEPs

The test was conducted using the *Hortmann* Brainstem Auditory Evoked Potentials audiometer in a sound-proof booth and in an electrically shielded room with the child sitting comfortably, sleeping or with eyes closed in order to eliminate the artifact caused by eye movement. Disposable electrodes Kedall model Meditrace 200 were positioned as follows: active electrode at Fz, reference electrode/ground position at M1 and M2 (left and right mastoids), to record the ipsilateral BAEP. The individual electrode impedance was less than 5 kΩ, and between electrodes, less than 2 kΩ. The click stimulus was presentedhrough a TDH-39 earphone at an intensity level of 80 dBHL, ith alternating polarity to reduce electrical artifacts, and presentation rate of 21.1 clicks/s, averaging 1000 stimuli in each collection, with bandpass filter of 30 and 3000 Hz. Wave reproducibility was used to identify the presence of responses. The first ear to be tested was randomly chosen. The absolute latencies of waves I, III, V, and the values of interpeak intervals I---III, III---V, and I---V were measured in milliseconds (ms).

Statistical Analysis—Descriptive statistical analysis was performed by considering the components of the BAEP recorded separately in eachar, lead levels in blood, and the estimated blood lead values. Considering the lack of certainty about the cumulative effect of lead on the auditory system, i.e., its influence in the long-term, the authors decided to study the possible influence of the duration of lead poisoning on the results ofthe BAEPs. For that purpose, the blood lead value estimated on the day of the audiological assessment was calculated having as reference the date when the first blood sample was collected from the population. The audiological assess-ment was performed at different times for each participant; however, within the period of blood lead level monitoring. During the study period, several measures were taken to prevent the children’s exposure to lead, and the data con-firmed that the levels of lead in blood decreased as a result of such interventions. Pearson’s correlation coefficient was calculated for the response variables (absolute latencies of waves I, III, and V and values of interpeak intervals I---III,III---V, I---V) and the independent variables (age, values of lead in blood obtained from collections made, and estimated blood lead values).Subsequently, a linear regression model was used for the right and left ears, using the absolute latency and interpeak values. Linear regression was the method used to select variables in the model, and the significance level was set at $p \leq 0.05$.

Results

In the present study, blood collection for the measurement of lead levels was performed four times throughout a period of 35 months; the results for each blood lead level (1stto 4th) are shown for each date of collection. The number of participants in each collection varied, despite efforts to include all participants on each occasion. The estimated blood lead level was 12.2 μg/dL (±5.7 μg/dL SD, ranging from 2.4 to 33 μg/dL SD). Table 1 shows the results of the descriptive statistical analysis (mean, standard deviation, median, minimum, and maximum values) of lead levels in blood obtained during the period of lead level monitoring and estimated blood lead levels.

A strong linear association between initial sample BPb results and the time of audiological evaluation was found ($r_{\text{Pearson's}}$ =0.78). The following variables were included in each subsequent model: latency of the waves I, III or IV, age, gender, time of audiological evaluation, and estimated blood levels on the date of audiological evaluation. To investigate the association of blood lead levels with BAER, the absolute latency of waves I, III and V (with wave III latency adjusted to wave I latency and wave V latency adjusted to wave III latency) were included in the model. The results of the initial regression of wave I absolute latency by ear in relation to age, gender, cumulative blood lead levels, and audiological evaluation date was not significant.

Table 2 shows the final model for the absolute latency of waves III and V (variables that did not show significant associations were not included in the Table). The absolute latencies and gender were the variables that reached significance. In this study, boys had higher latencies and interpeak intervals, with a significant difference when compared to girls.

Discussion

Concern about the effects of lead on health has led to several experimental and clinical studies conducted with industrial workers, adults, and children with a history of lead exposure. Lead levels in blood reflect the dynamic balance between absorption, retention, release, and elimination of the substance. In long-term exposure, this marker provides a reliable indicator of current exposure, unless the exposures vary widely, in which case the previous exposures will not be accurately reflected. In the present study, the reduction in the blood lead levels was observed over time, and the last two samples showed that the mean level of lead in the blood of the participants was lower than 10 μg/dL. The decrease in the blood lead levels in the studied children probably reflects the impact of measurements taken by the municipal government and by the company responsible for the contamination of the surrounding area. Even though the study was still in progress, the participants were treated due to lead poisoning, streets and public spaces near the battery factory were paved, and the affected population received information to avoid the consumption of local products from the community garden, as well as other information related to general health.

Although studies conducted with workers occupationally exposed to lead show consistent results indicating auditory effects, the data on the effects of environmental exposure to lead on the auditory system of children are contradictory (Holdstein et al, 1986, Osman et al, 1999; Counter et al, 1997a,b; Counter 2002; Zou et al, 2003). Schwartz and Otto (1987) suggested that evoked potentials procedures could provide early indication of lead contamination when compared to behavioral procedures, but subsequent studies (Counter et al, 1997a,b; Counter, 2002) and the present investigation failed to confirm such assertion.

The present study showed no association between low Blood lead levels values and absolute latencies and interpeak latencies obtained on the evaluation of brainstem auditory evoked potentials in children contaminated by lead. The model used (which included the variables age, estimated Blood lead levels, time between audiological evaluation and blood collection, and gender of the participants) revealed that the only significant association observed was between the absolute latencies of waves III and V and gender (Table 2). Boys had significant longer latencies and interpeak intervals when compared to girls, but the variations were unrelated to blood lead levels levels.

The association between gender and BAEPs absolute latencies was expected. The literature describes that auditory brainstem evoked potentials are affected by gender and age. The difference is explained by body and brain size differences between the genders. This finding is important when considering that, although some studies evaluate a control group and organized the control in a similar manner to that of the test group regarding gender and age, the statistical model often used to demonstrate the presence of a dose-effect relationship does not necessarily take into account the contribution of the independent variables of gender and age. Forst et al, (1997), for example, reported an association between the auditory function assessed and the level of lead in blood, however, after including age and gender in the statistical analysis, this correlation decreased.

Thus, unlike the results described by Otto et al (1985), Holdstein et al (1986), Osman et al (1999), Zou et al (2003), the present study found no association between the brainstem auditory evoked potentials and the cumulative blood lead levels, but in agreement to the findings obtained by Counter and colleagues in 1997(a, b) and in 2002. Lead levels of the present study were lower than in the above mentioned studies. The threshold and level of lead intoxication necessary to induce neuropathology have not been established. In Nordic Expert Group Criteria Document on Occupational Exposure to Chemicals and Hearing Impairment, Johnson & Morata (2010) identified the lowest observed adverse effect level (LOAEL) and the no observed adverse effect level (NOAEL) for lead for animals and humans specifically for auditory effects. A NOAEL of 35-40 μg/dL blood and a LOAEL of 55 μg/dL blood were identified for monkeys.

In human adults, central auditory effects have been associated with current exposures and life-time weighted average blood lead concentrations of approximately 28-57 μg/dL mostly from occupational studies. The present study did not observe auditory evoked potential abnormalities among children living in lead contaminated areas as 12.2 μg/dL.

Then results suggest that brainstem auditory evoked response is not the ideal procedure to examine children with low blood lead levels. Neurotoxicity appears to be the predominant mechanism underlying lead auditory effects (instead of ototoxicity). Considering this perspective, the recording of other evoked potentials or behavioral tests to investigate changes in central auditory processing appear to be more sensitive procedures for the early identification of lead-induced disorders, as described in the literature. The association between lead exposure and the central auditory processing skills was investigated1and higher lead levels in blood in the prenatal, neonatal, and post-natal periods were associated with poorer central auditory processing skills, as demonstrated by a filtered word test (screening test for auditory processing disorders [SCAN]).

However, the dichotic digits test and the auditory fusion test --- revised (AFTR) were used to evaluate a sub-sample of 20 children from the present study group, as a feasibility study. The children contaminated by lead showed lower performance in relation to clinical normative data; however, there was no correlation between blood lead levels and auditory processing skills. The long latency auditory evoked N2potential and cognitive P3 were also recorded in another sub-sample of 73 children.

The N2 potential latency increased with the concentration of lead in blood ($p = 0.030$), but no significant correlations were found between the concentrations of lead and latency ($p = 0.821$) or amplitude of the P3 potential ($p = 0.411$). Given that the N2 potential is endogenous and highly related to attention (McPherson and Ballachanda, 2000), this finding confirms that lead contamination can contribute to attention deficit, as previously reported (Bellinger, 2008). While different protocols of audiological assessment were performed in individuals exposed to solvents (Fuente, 2013), further studies are needed to identify the ideal procedures to assess the auditory effects of lead contamination. Evidence of effects of lead on cognition, including intelligence quotient (IQ), led the Center for Disease Control and Prevention to establish the level of lead in blood above 5 µg/dL as the population-based reference for children, aiming at primary preventive intervention (found online at http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf).

Conclusion

No association was observed between the wave components of the BAEP and the estimated blood lead levels of 12.2 µg/dL (±5.7 µg/dL) in children exposed to lead. BAEP does not seem to be the most sensitive method to evaluate children with low blood lead levels.

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Table 1

Descriptive statistics (mean, standard deviation, median, minimum and maximum) of the estimated blood lead levels (BPb) values, for males and females.

	n Males	Mean	SD	Median	Min	Max	n Females	Mean	SD	Median	Min	Max	n Total	Mean	SD	Median	Min	Max
																4.2	1.2	8.7
BPb in μg/dL																		
BPb1	94	17.1	6.7	15.1	10.0	44.2	62	16.5	11	14.0	10	90	156	16.9	8.6	14.6	10.0	90
BPb2	93	14.5	6.2	13.0	4.9	33.0	60	14.8	10.7	12.5	4.9	81.6	153	14.6	8.2	12.6	4.9	81.6
BPb3	87	9.0	4.8	7.8	0.0	26.5	57	9.3	9.1	7.4	2	68.2	144	9.1	6.8	7.6	0	68.2
BPb4	65	8.3	4.8	7.3	2.1	27.1	46	7.5	3.9	6.3	0	18.1	111	8	4.5	6.7	0	27.1
Estimated Cummulative Lead in μg/dL	80	**12.8**	6.2	10.9	4.4	33	50	**11.2**	4.6	9.6	2.4	23	130	**12.2**	5.7	10.2	2.4	33

Table 2

Results of the final multiple linear regression model for the Brainstem Auditory Evoked Potential (waves III and V absolute latencies) for the right (RE) and left ears (LE), for the male participants in comparison to the females.

Wave III, in relation to wave I	Coefficient	SE	p	Wave V, in relation to wave III	Coefficient	SE	p
Constant/ RE	4.004	0.017	0.000	Constant/ RE	5.770	0.016	0.000
Wave I RE	0.583	0.071	0.000	Wave III RE	0.810	0.066	0.000
Male/ RE	0.087	0.021	0.000	Male/RE	0.073	0.021	0.001
Constant/ LE	4.026	0.017	0.000	Constant/LE	5.782	0.015	0.000
Wave I LE	0.609	0.080	0.000	Wave III LE	0.850	0.059	0.000
Male/ LE	0.069	0.022	0.002	Male/LE	0.084	0.019	0.000