

The brainstem as a target of developmental methylmercury toxicity

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Abstract: Rodent experiments have documented neuropathological lesions specifically located in the brainstem when toxic methylmercury (MeHg) exposure occurs at a particular time during brain development. The possible sensitivity of the brainstem to MeHg was explored in the prospective study of a Faroese birth cohort (N = 1,022), most recently examined at age 14 years. In 878 of eligible children (87%), latencies of BAEP peaks I, III, and V at 20 and 40 Hz were recorded, as was heart rate variability (HRV) and its frequency components of autonomic origin. Mercury concentrations were available from analyses of cord blood and maternal hair at birth, and in the child's hair at ages 7 and 14. Latencies of peaks III and V increased at higher cord-blood mercury concentrations. At both age 7 and 14 years, this effect appeared mainly within the I-III interpeak interval (i.e. in the signal transmission to the pons). In regard to heart rate variability, increased methylmercury exposure was associated with decreases in the coefficient of variation of the R-R interval. The low-frequency component of this variability was significantly associated with increased latency of BAEP peak III, but adjustment for methylmercury exposure substantially attenuated this correlation. The persistence of prolonged I-III interpeak intervals and of decreased autonomic activation of the heart rate indicates that some neurotoxic effects from intrauterine methylmercury exposure are irreversible. Parallel exposure-related delays of BAEP latencies may be due to underlying MeHg neurotoxicity to brainstem nuclei. This suggests a neurotoxic mechanism involved in cardiovascular abnormalities and increased mortalities related to dietary MeHg exposure.

Key words: Epidemiology, Human Health, Neurotoxicity, Prenatal exposure

Introduction

The developing brain is thought to constitute the most vulnerable organ in regard to methylmercury exposure. Experimental studies suggest that the brainstem may be a sensitive target.^[1] Neurophysiological tests, such as assessment of brainstem auditory evoked potentials (BAEP), have found use in population studies as highly standardized, rapid, painless, and inexpensive procedures^[2]. Prolonged BAEP latencies have been reported as an effect of exposure to methylmercury and other neurotoxicants, such as lead. In contrast to neuropsychological test outcomes, this measure is thought to be

objective and independent of socioeconomic covariates. Another neurophysiological parameter that has been found to be sensitive to neurotoxicants, is heart rate variability (HRV), usually expressed as the coefficient of variation of the interval between R peaks of the electrocardiogram (CV-RR). A central origin of autonomic oscillations of the HRV is indicated by experimental data and by decreases in HRV parameters in relation to central damage of the brainstem nuclei associated with autonomic nervous function.

Both BAEP and HRV are known to be affected by methylmercury and depend on intact brainstem function. We previously showed that increased intrauterine mercury exposure was associated with delayed peak III latencies and decreased HRV at age 7 years. We hypothesized that changes would remain at age 14 and that these functions might also be sensitive to methylmercury from the adolescents' current seafood diets.

Results and Discussion

A cohort of 1,022 births was assembled in the Faroe Islands during a 21-month period of 1986-1987. The primary indicator of intrauterine exposure to methylmercury was the mercury concentration in cord blood, and concentrations in maternal hair at parturition were also determined. The first follow-up examination was carried out seven years later and included 913 children^[2]. At age 14 years, a total of 878 of 1,010 live cohort members were examined^[3,4]. Hair samples were obtained at both postnatal examinations and the proximal 2-cm segment was analyzed by flow-injection cold-vapor atomic absorption spectrometry after digestion of the hair sample in a microwave oven. A total of 18 children examined had neurological disorders thought to be independent of mercury exposure and were therefore excluded from the data analysis. Physical examination by a pediatrician included blood pressure measurement.

At both examinations, the heart rate was measured as the average R-R interval on an electrocardiographic amplifier connected to a computer. After the child had been lying in a relaxed, supine position and breathing normally for at least 5 min, 100 consecutive R-R intervals with the minimal standard deviation were automatically extracted for calculation of the average heart rate and its relative standard deviation (SD). The CV-RR is the ratio of the SD of the R-R intervals to the average value. The cardiac sinus rhythm shows fluctuations around the mean heart rate due to continuous changes in the autonomic balance. Fluctuations are mainly determined by respiratory sinus arrhythmia and baroreflex-related heart rate variation at a lower frequency. Their frequencies reflect the inspiratory inhibition of the vagal tone, and the slower rhythm originating from intrinsic oscillation in the vasomotor part of the baroreflex loop, and they therefore indicate parasympathetic and sympathetic activities. We applied autoregressive spectral analysis to partition the HRV into independent components of low frequency (LF) and high frequency (HF) components, i.e., 0.01-0.15 Hz and 0.15-0.40 Hz, and their CVs.

Latencies of peaks I, III, and V of the BAEPs were recorded by a four-channel electromyograph (Medelec Sapphire-4ME). Click signals at an intensity of 65 dB HL (0.1 ms impulses of alternating polarity) were presented to the right ear through shielded ear phones at 20 Hz and 40 Hz (sampling time, 0.01 ms); the other ear was masked with white noise at an intensity of 45 dB HL. Peaks I, III, and V are thought to reflect the

volume-conducted electric activity from the acoustic nerve, pons (superior olivary nucleus), and midbrain (inferior colliculi), respectively.

The prenatal exposure data showed an average that corresponded to the (previous) exposure limit recommended by WHO, i.e., an average maternal hair-mercury concentration of slightly more than 4 µg/g. Hair-mercury concentrations at age 14 years indicated that approximately half of the children exceeded the hair-mercury limit of 1 µg/g (the exposure limit of the U.S. Environmental Protection Agency), i.e., only one-fourth of the concentrations in maternal hair at child birth.

At both examinations, the CV-RR and its HF and LF components appeared affected by mercury, though the LF less so at age 7 years. Despite significant associations between exposure indicators and several HRV outcomes, a mercury effect on blood pressure was documented at age 7 years but was not discernible at age 14 years. The significant associations of 14-year outcomes with prenatal mercury exposure were attenuated after adjustment for the 7-year outcomes.

Table 1. Sex-adjusted partial correlation coefficients (p value) for paired results of BAEP peak latency III in relation to cardiovascular parameters at the 14-year examination, before and after additional adjustment for mercury exposure.

Outcome	Sex adjusted	Adjusted also for mercury
CVRR*	-0.01 (0.67)	0.00 (0.95)
LF power*	-0.06 (0.073)	-0.04 (0.33)
HF power*	0.03 (0.37)	0.03 (0.43)
LF / HF*	-0.11 (0.002)	-0.07 (0.040)
C-CVLF*	-0.09 (0.009)	-0.06 (0.11)
C-CVHF*	0.01 (0.86)	0.01 (0.79)

* **Log transformed**

A delay in peak III of the BAEP was seen both at age 7 and at age 14 in relation to increased prenatal methylmercury exposures. Peak V showed a delay associated with the current exposure level and not with the prenatal exposure. The only statistically significant covariate was sex, which was not associated with the exposure levels. PCB exposure was not associated with the BAEP latencies or with HRV.

To ascertain possible associations with brainstem functions, correlations were calculated with the latency of BAEP peak III, which appears to be increased by prenatal MeHg exposure. The LF power and its component CV showed clear negative associations with peak III latencies, viz., the greater the BAEP latency, the less the LF

power and its CV (Table 1). To determine whether these associations were innate, partial correlation coefficients were calculated with adjustment for prenatal and postnatal MeHg exposure biomarkers. These adjusted correlations were substantially attenuated and tended to lose statistical significance.

Conclusions

A link between brainstem functions and autonomic tone is supported by the associations in the present study between BAEP latencies and HRV parameters, especially the LF results. Although only weak and mostly non-significant after adjustment for mercury exposure, the possibility cannot be completely discounted that such correlations are normal and unrelated to neurotoxicant exposures. However, the fact that methylmercury exposure affects both parameters would suggest that the exposure-related changes in HRV at least in part reflect mercury neurotoxicity exerted in the brainstem nuclei.

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