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Review

Neurophysiological Evidence of Methylmercury Neurotoxicity

Katsuyuki Murata, MD, DMSc,[1]* Philippe Grandjean, MD, DMSc,[2,3] and Miwako Dakeishi, PhD[1]

Background *A variety of neurophysiological measures are useful in hospital settings for diagnostic and other clinical purposes. Previously, abnormal changes in various sensory evoked potentials (EPs), and heart rate variability (HRV) were observed in patients with acquired and fetal Minamata disease (MD; methylmercury poisoning). In recent years, some of these methods have been used for the risk assessment of low-level methylmercury exposure in asymptomatic children. The objectives of this article were to present an overview of neurophysiological findings involved in methylmercury neurotoxicity and to examine the usefulness of those measures.*

Methods *The reports addressing both neurophysiological measures and methylmercury exposure in humans were identified and evaluated.*

Results *The neurological signs and symptoms of MD included paresthesias, constriction of visual fields, impairment of hearing and speech, mental disturbances, excessive sweating, and hypersalivation. Neuropathological lesions involved visual, auditory, and post- and pre-central cortex areas. Neurophysiological changes involved in methylmercury, as assessed by EPs and HRV, were found to be in accordance with both clinical and neuropathological observations in patients with MD.*

Conclusions *EPs and HRV appear to be useful and objective methods for assessing methylmercury neurotoxicity. However, subtle changes due to low-level methylmercury exposure may not necessarily be of clinical relevance, and interpretation of small deviations from expectations must be cautious.* Am. J. Ind. Med. 50:765–771, 2007.

KEY WORDS: methylmercury; prenatal exposure; neurophysiological measures; children; review

INTRODUCTION

Minamata disease (MD) is an intoxication involving the central nervous system, which developed among the inhabitants frequently ingesting large quantities of fish and shellfish contaminated with methylmercury discharged by a chemical plant [Social Scientific Study Group on Minamata Disease, 1999]. The diagnosis of MD was usually not difficult in typical and severe cases, but more difficult in mild cases [Igata, 1993]. Thus, clinical and objective methods would be crucial for evaluating borderline cases of possible MD.

The introduction of electronic technologies in neurotoxicology, such as sensory evoked potentials (EPs), event-related potentials (ERPs), and heart rate variability (HRV), has enabled specific evaluation of central, peripheral or

[1]Department of Environmental Health Sciences, Akita University School of Medicine, Akita, Japan
[2]Department of Environmental Medicine, Institute of Public Health, University of Southern Denmark, Odense, Denmark
[3]Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts

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*Correspondence to: Katsuyuki Murata, Department of Environmental Health Sciences, Akita University School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan.
E-mail: winestem@med.akita-u.ac.jp

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autonomic nervous system dysfunction [Araki et al., 1994, 1997]. These neurophysiological methods have proven useful in hospital settings for diagnostic and other clinical purposes (e.g., monitoring during surgery) [Chiappa, 1997]. In epidemiological studies of methylmercury-exposed populations, these methods may complement neurological tests and neuropsychological tests that may be more easily affected by socioeconomic conditions and examiner variables.

When results from population-based studies on developmental methylmercury neurotoxicity became available, a workshop of experts was organized at the request of the White House in November 1998 [Committee on Environmental and Natural Resources, 1999]. The study conclusions appeared equivocal in regard to the potential health effects of methylmercury, and a key to determine whether or not low-level methylmercury exposure harms the fetus might then depend on neurophysiological confirmation from parameters, such as EPs and HRV [Murata and Dakeishi, 2005].

During the last dozen years or so, neurophysiological methods have been used for the risk assessment of low-level methylmercury exposure in asymptomatic children [Grandjean et al., 1997, 2004; Murata et al., 1999a,b, 2004a,b, 2006]. These neurophysiological findings must be validated against data obtained from clinical cases of methylmercury poisoning. This paper therefore examines the usefulness of the above methods in environmental and occupational health, with emphasis on methylmercury neurotoxicity.

CLINICAL AND PATHOLOGICAL FINDINGS OF MINAMATA DISEASE

Japanese patients with acquired MD had neurological signs and symptoms, such as paresthesias, constriction of visual fields, hearing loss, speech disorders, psychological disturbances, disordered handwriting, unsteady gait, intention tremor, and excessive sweating and salivation [Kurland et al., 1959; Uchino et al., 1995]. Also, the symptoms of fetal MD were essentially similar to those of acquired MD whereas peripheral neuropathy was not manifest as a cardinal symptom; and, mental retardation with symmetrical motor disturbance was rather characteristic [Igata, 1993]. Likewise, poisoned Iraqi children had mental retardation with delayed onset of speech and impaired motor, sensory, and autonomic function [Bakir et al., 1980].

Pathological lesions in patients with acquired MD mainly involved visual, auditory, and post- and pre-central cortex areas; cerebellar atrophy of granule-cell type was shown [Takeuchi et al., 1962; Igata, 1993]. In mild cases, the lesions tended to localize in the area striata of the occipital lobe and postcentral gyrus. Also, there was either significant loss of small myelinated fibers or decrease of large neurons in the cochlear nerve, ventral cochlear nucleus, and inferior colliculus, in addition to degeneration of the transverse temporal gyrus [Oyanagi et al., 1989]. In patients with fetal MD, pathological lesions generally were more widespread, though synapses in the cellebellum were well-preserved [Eto et al., 1992]. Thus, these clinical and pathological findings suggest that methylmercury toxicity leads to somatosensory, visual, auditory, and autonomic nervous system dysfunction.

PREVIOUS EVIDENCE ON MINAMATA DISEASE

Short-latency somatosensory evoked potentials (SSEPs) are recorded from the scalp by way of electric stimulation of a sensory nerve in the upper extremity (e.g., median nerve); in this case, the neural origins of the N9, N11, N13, and N19 peaks are considered to be generated from the brachial plexus, from the posterior columns in the spinal cord, from the central cord gray matter (dorsal horns), and from the primary sensory cortex or the thalamus, respectively [Chiappa and Hill, 1997]. In the patients with acquired MD, who had a bilateral, symmetric, low-density area in the visual cortex and diffuse atrophy of the cerebellar hemispheres and vermis in computerized tomography, the N19 peak of the SSEP was absent, while N9, N11, and N13 peaks were observed [Tokuomi et al., 1982]. In patients with fetal MD, a significant prolongation of N13–N19 interpeak latency was recorded, thus indicating a delayed central conduction time of the somatosensory pathway [Inayoshi et al., 1988]. Also, the thresholds of two-point discrimination increased at both the lip and forefingers in patients with acquired MD and the fishermen residing in nearby communities at the Shiranui Sea beyond the Minamata Bay, as compared to the age-matched controls [Ninomiya et al., 2005]. On the other hand, methylmercury-poisoned rats showed markedly decreased amplitudes, while the latencies were normal for the potentials evoked in the spinal dorsal roots [Arimura et al., 1988]. Thus, these findings suggest that the somatosensory pathway from the gracile and cuneate nuclei to the primary sensory cortex was impaired by both postnatal and prenatal exposures to methylmercury, and that clinical paresthesias in these patients may be linked with a central somatosensory impairment.

The visual evoked potential (VEP) latencies reflect the neurological function of the long pathway between the retina and visual cortex [Araki et al., 1994, 1997]. Imai et al. [1991] measured the pattern-reversal VEPs in patients with acquired MD and control subjects, indicating a significantly prolonged P100 latency of the VEP in the patients. Also, Iwata [1980] reported pronounced effects on the waveform, amplitude, and latency of flash VEPs in patients suffering from methylmercury poisoning.

In recording brainstem auditory evoked potentials (BAEP), sometimes referred to as the auditory brainstem response, click stimuli are presented monaurally at a rate of 20 or 40 Hz through shielded earphones. The peaks of I, III,

and V primarily represent volume-conducted electrical activities from the acoustic nerve, pons, and midbrain, respectively [Stockard et al., 1986]. When the BAEPs were assessed in patients with fetal MD, the I–III and I–V interpeak latencies were significantly delayed in the patients, compared to the control subjects, but a significant difference in the III–V interpeak latency was not found between the two groups [Hamada et al., 1982].

The long-latency EPs related to aspects of cognitive processing are referred to as cognitive EPs or endogenous ERPs [Oken, 1997]. The most commonly used method to obtain the ERP (especially P300) is referred to as the ''oddball'' paradigm, involving the presentation of unexpected or infrequent stimuli randomly interspersed among more frequent stimuli. The P300 latency with auditory stimulation was significantly delayed in 10 cases with acquired MD, as compared with 15 healthy controls [Kondo et al., 1995].

Short-term variations in heart rate are seen at all ages and are an important sign of normal homeostatic mechanisms of the cardiovascular system [Finley and Nugent, 1995]. Especially, HRV with frequency-domain analysis has emerged as a non-invasive method to assess cardiac autonomic activities quantitatively and is highly reproducible under standardized conditions [Massin and von Bernuth, 1997; Batten et al., 2000]. According to previous studies, the high-frequency (HF) and low-frequency (LF) components are thought to reflect mainly the parasympathetic and sympathetic activities, respectively [Pagani et al., 1986; Murata and Araki, 1996; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996]. In a clinical study, the HF component of HRV parameters was significantly lower in patients with fetal MD than in the control subjects, thus implying that these patients had parasympathetic hypoactivity [Oka et al., 2002].

RECENT RESEARCH IN METHYLMERCURY-EXPOSED CHILDREN

Exposure Levels in Study Populations

Several reports have appeared on neurophysiological effects of methylmercury in children without any clinical sign of MD. The exposure levels are lower than in the poisoning incidents and overlap with those commonly occurring in fishing populations. In the Faroe Islands, the mothers of the 1,022 cohort children had hair-mercury levels between 0.2 and 39.1 μg/g (median 4.5 μg/g) at parturition [Grandjean et al., 1992]. In the children followed-up at ages 7 and 14 years, the geometric means of the hair-mercury concentrations were 2.99 μg/g (interquartile range, 1.69–6.20 μg/g) and 0.96 μg/g (0.45–2.29 μg/g), respectively [Murata et al., 2004b]; the decrease in hair-mercury concentrations may be due to the dietary advisory issued by Faroese health authorities in August 1998 [Weihe et al., 2005]. In Madeira, hair-mercury concentrations were between 0.38 and 25.95 μg/g (median 4.09 μg/g) in 149 children at age 7 years and 1.23 – 54.5 μg/g (median 10.9 μg/g) in the mothers [Murata et al., 1999b]; the latter levels were used as a proxy for mercury exposure at birth. In a small Greenland study, hair-mercury levels in 43 Inuit children at age 6.2–12.0 years (median 8.4 years) varied up to 18.4 μg/g (geometric mean, 5.5 μg/g), while 31 maternal hair samples showed a maximum mercury concentration of 32.9 μg/g (geometric mean, 15.5 μg/g) [Weihe et al., 2002]. In Akita and Tottori prefectures of Japan, hair-mercury concentrations ranged from 0.35 to 6.32 μg/g (median 1.65 μg/g) in 327 children at age 7 years and from 0.11 to 6.86 μg/g (median 1.63 μg/g) in their mothers [Murata et al., 2004a]. Thirty-one Andean children, aged 4–14 years, of gold miners living in the Ecuadorian gold mining settlement of Nambija had blood mercury levels (BHg) of 23.0 ± 19 (mean $\pm$ SD) μg/L (range, 2.0–89.0 μg/L) [Counter, 2003].

VEP Findings

The VEPs were measured in the Faroese birth cohort study, the Madeiran study, and the Inuit study by a single experienced examiner [Grandjean et al., 1997; Murata et al., 1999b; Weihe et al., 2002]. Although all the studies failed to observe any significant associations between methylmercury exposure and VEP latencies, the maternal hair-mercury concentration was associated with the greatest relative increase of the N145 latency on the 30-min pattern on a population basis. The means and standard deviations (SDs) of the N145 latency after adjustment for age and sex were 151.6 ± 12.2 ms in the Inuit group, 143.7 ± 11.6 ms in the Madeiran group, and 140.4 ± 13.2 ms in the Faroese group [Weihe et al., 2002]. VEP latencies are known also to be affected by nutritional factors, including the supply of essential fatty acids, during early development [Jensen et al., 1997]. Nutritional factors, for example, docosahexaenoic acid originating from fish, were not assessed in the above studies, and confounder adjustment could therefore not be performed. However, since all three population groups had a high seafood intake, the cross-study comparison may suggest that a mercury effect is present, while not detectable within the individual studies.

BAEP Findings

In 7-year-old children from the Faroese birth cohort, delays of the peak III latency and the I–III interpeak latency of the BAEP were significantly associated with intrauterine methylmercury exposure biomarkers including the cord blood mercury concentration, while such associations

were not apparent in regard to the current hair-mercury concentration in the children [Murata et al., 1999a]. Also, results of BAEPs measured in the children at age 14 years were similar to those obtained at age 7 years [Murata et al., 2004b]; that is, exposure biomarkers at birth showed positive associations with the peak III latency and the I–III interpeak latency. In addition, the III–V interpeak latency was significantly related only to the hair mercury concentration in the children at age 14 years, thus suggesting that postnatal exposure affected this outcome [Murata et al., 2004b].

The BAEP results in the Madeiran study [Murata et al., 1999b] were in close accordance with those from the Faroes [Murata et al., 1999a]. However, the smaller Greenland study and the Japanese study did not reveal any significant dose-effect relationships [Weihe et al., 2002; Murata et al., 2004a]. Again, the III–V interpeak latency in the Inuit children tended to be prolonged as compared to those in the Madeiran children and the Faroese children [Weihe et al., 2002]. A similar comparison in the BAEP latencies was made between the Madeiran and Japanese children, the former group having considerably higher maternal hair mercury concentration than the latter; the peak III and V latencies (and the III–V interpeak latency) were significantly delayed in Madeira [Murata et al., 2004a]. Thus, both within populations and between populations subtle changes in BAEP latencies seem to reflect neurotoxic effects of the developmental methylmercury exposure.

In 31 Andean children, the III–V and I–V interpeak latencies of the BAEP showed significant prolongation, as compared to 21 control children, aged 2–15 years, with the BHg of 4.5 ± 2.3 μg/L (range, 1–10 μg/L) [Counter, 2003]. Also, the BAEP measures showed significant positive correlations between the BHg and the peak V latency and the I–V interpeak latency in the Andean children. Regrettably, the author did not consider the effects of possible confounders such as age and sex.

HRV Findings

Among the Faroese children, the LF and HF components of the HRV were negatively associated with the mercury levels in cord blood [Grandjean et al., 2004], while the postnatal hair-mercury concentration at ages 7 or 14 years was not significantly related to any HRV parameters. In Japanese children at age 7 years, the methylmercury concentration in umbilical cord tissue, but not the hair-mercury level at age 7 years, was significantly linked with decreases of the HF component of the HRV [Murata et al., 2006]. The maternal hair-mercury levels at parturition were estimated to be between 0.43 and 9.26 μg/g (median 2.24 μg/g) according to the equation of Akagi et al. [1998]. These results are consistent with the result of patients with fetal MD [Oka et al., 2002], although the relative effect on the LF component is somewhat unclear. The mercury concentration in cord blood and the methylmercury concentration in cord tissue appeared to be better markers of HRV changes than the maternal hair-mercury level at parturition [Grandjean et al., 2004, 2005; Murata et al., 2006].

DISCUSSION

In the past, the lack of standardized recording and analysis techniques for EP measures sometimes generated contradictory results [Arezzo et al., 1985]. However, neurophysiological methods, such as EPs, ERPs, and HRV, have been carefully standardized since then [Araki et al., 1994, 1997; Daube, 1996; Murata and Araki, 1996; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Chiappa, 1997] and have been extensively used clinically. These methods require relatively expensive equipment and highly trained staff to administer the procedures, and score and interpret the results, and they also depend on reliable electrical power. In regard to quality assurance, the Faroes study showed a coefficient of variation below 10% for latencies of VEPs and BAEPs [Grandjean et al., 1997; Murata et al., 1999b, 2004b]. Accordingly, the reproducibility of these methods is amply documented, and they appear to represent reliable and non-invasive methods that may be suitable for studies of pediatric populations. Also, although neurophysiological test results are apparently independent of socioeconomic parameters that may constitute important confounders for neuropsychological tests, the developmental stage may play a role [Chiappa, 1997], and both age and sex would then be mandatory covariates for adjustment in the statistical analysis. In addition, personal habits, such as tobacco smoking and alcohol drinking, can play a role in adults and must be taken into account [Araki et al., 1994, 1997].

Most of the recent dose-effect findings on neurophysiological parameters in children prenatally exposed to methylmercury, as shown in Table I, were consistent with the evidence obtained from case-control studies on patients with acquired or fetal MD, where individual exposure data were unavailable. In addition, the combined results on EPs and HRV were in accordance with both clinical and neuropathological observations in MD patients [Kurland et al., 1959; Takeuchi et al., 1962; Oyanagi et al., 1989; Igata, 1993; Uchino et al., 1995]. Thus, the neurophysiological measures provide an objective means of elucidating possible abnormalities at exposure levels that may only cause subclinical damage. Still, the long-term consequences of minor delays in EP latencies and of small decreases in HRV are difficult to assess at present and may require joint consideration of neurophysiological, neuropsychological, and clinical neurological findings.

TABLE I. Neurophysiological Findings on Methylmercury Neurotoxicity in Humans

Outcome parameters	Exposure	Effects[a]	References
Somatosensory evoked potentials (mainly, N19 latency)	Prenatal	D (MD)	Inayoshi et al. [1988]
	Postnatal	C (MD)	Tokuomi et al. [1982]
Visual evoked potentials	Postnatal	D (MD)	Iwata [1980]; Imai et al. [1991]
	Pre- and postnatal	D (CS)	Weihe et al. [2002]
Brainstem auditory evoked potentials			
I–III interpeak latency	Prenatal	D (MD), A (Co)	Hamada et al. [1982]; Murata et al. [1999a, 2004b]
III–V interpeak latency	Pre- and postnatal	D, A (CS)	Weihe et al. [2002]; Counter [2003]; Murata et al. [2004a]
	Postnatal	A (Co)	Murata et al. [2004b]
Event-related potential (P300)	Postnatal	D (MD)	Kondo et al. [1995]
Heart rate variability	Prenatal	D (MD), A (Co)	Oka et al. [2002]; Grandjean et al. [2004]; Murata et al. [2006]

[a]The effect was expressed as significant difference (D), remarkable change in the waveform (C) or significant association with methylmercury (A) among cases with Minamata disease (MD) and children of the cross-sectional (CS) or cohort (Co) study.

The effects on BAEP associated with methylmercury exposure differed from the one on SSEP in respect of the period of vulnerability. Thus, SSEP abnormalities in patients with fetal MD appeared to be similar to those in patients with acquired MD. In contrast, the delayed BAEP latency differed between prenatal and childhood exposures (i.e., peaks III and V, respectively) [Hamada et al., 1982; Murata et al., 1999b, 2004b]. Similarly, significant findings obtained from the Ecuadorian children with increased current exposures regarded the peak V latency and III–V interpeak latency of the BAEP [Counter, 2003]. Therefore, the auditory pathway from the acoustic nerve to the pons may have been permanently affected by prenatal methylmercury exposure (i.e., its effect seems to have lasted at least for 14 years) and the change in the auditory pathway from the pons to the midbrain may have been sensitive to more recent methylmercury exposure at adolescence. Whether such functional damages in the brain due to the low-level exposure are completely irreversible awaits further long-term prospective research.

The neurophysiological effects of methylmercury, as in the case of lead [Araki et al., 2000], appear mainly associated with delays in nerve conduction, that is, deceleration in neural circuits. The neurobehavioral effects involved in prenatal methylmercury biomarkers in the Faroese children [Grandjean et al., 1997; Debes et al., 2006] were deficits in finger tapping speed, reaction time on a vigilance task, and cued naming (i.e., deceleration of time-dependent performance). Regarding these results, the benchmark dose levels (BMDL), that is, the critical concentrations affecting the brain, of methylmercury for the neurophysiological effects [Murata et al., 2002, 2004a,b] were almost similar to those for the neurobehavioral effects [Budtz-Jørgensen et al., 2000, 2004]. A similar result was obtained from intelligence test (WISC-R) data in a mercury-exposed population from New Zealand [Crump et al., 1998]. High-level exposure is known to cause mental retardation with motor disturbance, and sometimes fatal encephalopathy [Igata, 1993]. Thus, this implication is that neurophysiological and neurobehavioral findings due to methylmercury or lead at low exposure levels represent the initial signs involved in lifelong loss of intelligence and permanent disruption of behavior that may produce reduction of economic productivity [Landrigan et al., 2002].

The effect of methylmercury at low exposure levels may be hidden by effects of confounders, unless proper adjustment is achieved. The changes in EP parameters are relatively small, even in patients [Hamada et al., 1982; Inayoshi et al., 1988; Imai et al., 1991; Oka et al., 2002] and may be apparent only in large population groups. Thus, the neurophysiological measures alone would not be suitable for determining whether or not an individual patient should be diagnosed with methylmercury poisoning, especially if exposure data are absent. Given the health significance and economic importance of optimal brain function, even asymptomatic dose-dependent changes should be considered as an important indication that methylmercury neurotoxicity at low exposure levels is adverse to health.

In conclusion, the neurophysiological findings on the effects of methylmercury are in good accordance with both the clinical and neuropathological observations in MD patients. Because of this consistency, neurophysiological measures, especially BAEP and HRV, are promising and useful for epidemiological research, and further supported by their independence of language or education [Weihe et al., 2002; Murata et al., 2004a]. In contrast to neuropsychological tests, which are often culture-dependent, the neurophysiological tests will also allow direct comparison between children from different populations, if comparable and standardized measures are employed in each study. Since neurophysiological evidence of methylmercury neurotoxicity is limited in the literature (Table I), further research is necessary to confirm it.

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