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Associations between prenatal and recent postnatal methylmercury exposure and auditory function at age 19 years in the Seychelles Child Development Study

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ABSTRACT

Objectives: The aim of this study was to determine if prenatal or recent postnatal methylmercury (MeHg) exposure from consuming ocean fish and seafood is associated with auditory deficits in young adults. Some investigators have reported adverse associations while others have found no associations. Ocean fish is an important nutrient source for billions of people around the world. Consequently, determining if there is an adverse association with objective auditory measures is important in assessing whether a risk is present or not.
Design: The peripheral and central auditory function of 534 subjects in the Seychelles Child Development Study (SCDS) Main Cohort was examined at age of 19 years. The auditory test battery included standard pure-tone audiometry, tympanometry, auditory brainstem response (ABR) latencies, and both click-evoked and distortion-product otoacoustic emissions (OAE). Associations with MeHg were evaluated with multiple linear regression models, adjusting for sex, recent postnatal MeHg exposure, and hearing loss.
Results: Bilateral hearing loss (defined as a mean pure-tone threshold of greater than 25 dB) was present in 1.1% of the subjects and was not associated with prenatal or recent postnatal MeHg exposure. As expected, absolute and interwave ABR latencies were shorter for women as compared to men, as the stimulus presentation rate decreased from 69.9 to 19.9 clicks/s and as the stimulus intensity increased from 60 to 80 dBnHL. Similarly, larger OAE amplitudes were elicited in women as compared to men and in the right ears as compared to the left. There was no association of prenatal MeHg exposure with hearing loss, ABR absolute and interwave latencies or OAE amplitudes. As recent postnatal MeHg increased, some associations were found with a few ABR absolute and interwave latencies and a few OAE amplitudes. However, the direction of these associations was inconsistent. As recent postnatal MeHg levels increased the wave I absolute latencies were shorter at 80 dBnHL for all three click rates, but the interwave I–V latency was longer for males for the 80 dBnHL 19 clicks/s and for the III–V interwave latencies for males and females for the dBnHL 69 clicks/s. Similarly, smaller OAE amplitudes were found at 1500, 2000, and 4000 Hz for males while larger OAE amplitudes were found for females at 1500 and 2000 Hz as the recent postnatal MeHg levels increased.
Conclusions: No consistent associations were present in this study between prenatal MeHg exposure from consumption of oceanic fish and seafood during pregnancy and auditory functions at 19 years of age. Given the

Abbreviations: ABR, Auditory brainstem response; CEOAE, Click evoked otoacoustic emission; DPOAE, Distortion product otoacoustic emission; Hg, Mercury; LCPUFA, Long chain polyunsaturated fatty acids; MeHg, Methylmercury; OAE, Otoacoustic emission; OHC, Outer hair cells; PCB, Polychlorinated biphenyl; THg, Total mercury.

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level of prenatal exposure to MeHg, the number of audiologic measures tested, and the presence of the expected sex, click rate, and level dependent findings, it seems unlikely that an association was present and not detected. As recent postnatal MeHg exposure increased, a few associations with ABR latencies and OAE amplitudes were found. The direction of these associations was inconsistent as some showed improved performance as MeHg exposure levels increased while others showed poorer performance. The presence of the inconsistent postnatal MeHg exposure findings are intriguing and deserve further clarification.

1. Introduction

Methylmercury (MeHg) is a neurotoxicant that adversely affects central nervous system function in adequate doses (Clarkson, 1995). Human exposure to MeHg is widespread, almost exclusively from consuming fish, and at dosages substantially below those known to cause signs or symptoms of poisoning. All fish contain small amounts of MeHg. In aquatic environments, bacteria transform inorganic mercury (Hg) into MeHg which is then bio-accumulated up the aquatic food chain. Large predatory fish can bio-accumulate MeHg up to 1.0 ppm or greater (WHO, 1990).

The developing nervous system is especially sensitive to MeHg exposure as demonstrated by observational studies of poisoning and experimental studies. The auditory system is an optimal organ system with which to detect subtle peripheral and central neurological effects. The measurement of peripheral end-organ function (inner hair-cell function) can be assessed with otoacoustic emissions (OAE) and central nervous system (CNS) auditory processing function (auditory nerve conduction speed) with auditory brainstem responses (ABR). These can be directly measured and appear to be independent of each other (Lonsbury-Martin and Martin, 1990; Moore et al., 1995).

Auditory brainstem responses represent the summed electrical potentials of sequential activation in the auditory system in response to a repeated stimulus such as a tone burst or click. The ABR waveform has distinct peaks and troughs and represents the summed action potential propagating from the auditory nerve through the cochlear nucleus to the inferior colliculus (Moller et al., 1982).

ABR latencies have been shown to correspond to the degree of myelination in the auditory pathway (Moore et al., 1995; Knipper et al., 2000; Ito et al., 2004), as well as providing information on synaptic maturation and axonal structure (Rance, 2005; Wang and Manis, 2005). For example, broader response peaks and prolonged latencies were found in animal models with myelin deficiencies (Naito et al., 1999; Ito et al., 2004; Roncagliolo et al., 2000; El-Badry et al., 2007). In addition, neurofilament deficiencies and altered axonal structure also have been shown to prolong latencies (Sheykholeslami et al., 2001; Jones et al., 2008).

ABRs have been used to quantify damage to the developing auditory system caused by high dosages of neurotoxicants such as heavy metals and organic compounds (see Dyer, 1985; Otto et al., 1988). A few adults with Minamata disease have shown hearing loss or elevated hearing thresholds as a clinical feature of accidental poisoning (McAlpine and Araki, 1958; Kurland et al., 1960; Nosaka et al., 1970; Fujisaki et al., 1971; Mizukoshi et al., 1975; Ino and Mizukoshi, 1977). Prolonged ABR latencies were also reported in patients diagnosed with Minamata disease, although exposure verification was not possible (Hamada et al., 1982; Inayoshi et al., 1993).

Inconsistent and sporadic associations between certain absolute and interwave latencies and prenatal MeHg exposure from the consumption of oceanic fish and sea mammals have been reported in populations in the Faroe Islands, Greenland, Japan, and Madeira. Some studies have reported prolonged ABR latencies (Grandjean et al., 1997; Murata et al., 1999a,b, 2004a), while others have found no association (Weihe et al., 2002; Murata et al., 2004b). In these studies various metrics of prenatal MeHg exposure were used including cord blood or maternal hair samples taken at birth (Grandjean et al., 1997; Murata et al., 1999a, 2004a) or during testing when the children were several years of age (Murata et al., 1999b, 2004b). These studies have not been replicated to date in a population in which the source of MeHg exposure was primarily from consumption of oceanic fish, the entire period of prenatal exposure was characterized and there was minimal or no exposure to other contaminants.

To our knowledge no human studies have used the OAEs to examine the peripheral cochlear function in a cohort of individuals exposed to low dose MeHg (Dziorny et al., 2012). Otoacoustic emissions (OAEs) provide a quantitative assessment of the function of the peripheral auditory system (outer hair cells), which cannot be obtained by measuring ABRs alone. Otoacoustic emissions measure sound pressure variations in the ear canal and are thought to reflect induced movement of the basilar membrane by outer hair cells (OHCs) (Kemp et al., 1990; Lonsbury-Martin and Martin, 1990). The amplitude of OAEs is decreased or absent when OHCs are missing or not functioning properly (Liberman et al., 2002; Colombari et al., 2011). For example in experimental animals, polychlorinated biphenyl (PCB) exposure has been shown to decrease the amplitude and increase the threshold of distortion product OAEs (DPOAE) (Lasky et al., 2002). In addition, environmental noise exposure can disrupt auditory function causing both threshold shifts in ABRs and reduced amplitude OAEs (Daniel, 2007; Marshall et al., 2009).

High dose exposure to MeHg can be very toxic to not only the auditory system but the entire neurological system and even cause death. A few studies of subjects exposed to multiple toxicants have reported an association of low level MeHg exposure and psychometric outcomes after adjusting statistically for other contaminants (Grandjean et al., 1997; Debes et al., 2006; Boucher et al., 2014). However, studies of subjects consuming oceanic fish and not contaminated with other known toxicants have not confirmed these low level associations (Davidson et al., 2011; Llop et al., 2012: Strain et al., 2012). This study evaluated the association between a subject's prenatal and recent postnatal MeHg exposure and the peripheral and central auditory function in participants enrolled in the Seychelles Child Development Study Main Cohort at 19 years of age. This study tested subjects with common hearing evaluation procedures as well as both ABR and OAE testing procedures to determine if prenatal or recent postnatal exposure to MeHg primarily from ocean fish consumption is associated with changes in auditory function.

2. Methods

2.1. Study population and MeHg measurements

The SCDS is a longitudinal cohort study in a population which is exposed to MeHg from ocean fish and seafood consumption (Marsh et al., 1995). Sea mammals are not consumed in Seychelles. At enrollment of the Main Cohort, mothers reported consuming on average 12 fish meals per week. The cohort consists of 779 mother–infant pairs that were enrolled in 1989–1990 (Marsh et al., 1995). Eighty-two subjects were excluded for specific reasons including lack of maternal hair for exposure assessment, medical conditions affecting development or study withdrawal (Myers et al., 2003). At 19 years of age there were 697 young adults (89.5%) eligible for this study. A total of 534 subjects (76.6% of the eligible cohort) participated in this evaluation. Their ages