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Cognitive function and blood methylmercury in adults living near a deserted chloralkali factory

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ABSTRACT

We assessed the association between blood methylmercury (MeHg) and cognitive function in 240 adult residents living near a deserted chloralkali plant. Total mercury (T-Hg) in the blood, MeHg, and health and dietary related questionnaire were examined for all participants. The Cognitive Abilities Screening Instrument (CASI C-2.0) and Mini-Mental State Examination (MMSE) were used to assess the participants' cognitive functions. We found a significantly high correlation ($r = 0.979$; $p < 0.001$) between blood T-Hg ($17.3 \pm 10.9\,\mu g/L$) and MeHg ($15.3 \pm 9.2\,\mu g/L$). We also found significantly higher blood MeHg levels in participants with high local fish and seafood consumption, which revealed that dietary intake was the major exposure route of MeHg. All the participants were assigned to the high-MeHg (H-MeHg, $27.0 \pm 10.4\,\mu g/L$) or low-MeHg (L-MeHg, $11.6 \pm 4.7\,\mu g/L$) groups based on the 75th percentile of their blood MeHg ($19.2\,\mu g/L$), and then matched for cognitive function confounders: age, gender, and education levels. Higher abnormality rates for remote memory ($p = 0.036$), mental manipulation ($p = 0.013$), and orientation ($p = 0.005$) were found in the H-MeHg group than in the L-MeHg group. Long-term consumption of MeHg-contaminated fish and seafood by residents living near this contaminated area may have persistent effects on their cognitive function. We suggest a follow-up study to monitor the long-term health effects on the residents living near this deserted plant.

1. Introduction

Methylmercury (MeHg) exposure is of particular concern because it is a well-known human neurotoxicant and it may give rise to neurobehavioral disorders (Dolbec et al., 2000; WHO/IPCS, 1989, 1990a, b). Tragic instances of MeHg poisoning have already occurred, viz. in Niigata and Kumamoto (Minamata City) Prefectures, Japan (Harada, 1995; Tsubaki and Irukayama, 1977), and in Iraq (Bakir et al., 1973). These disasters revealed that the nervous system is a primary target of organic mercury poisoning, involving disturbances of sensation in the extremities, paresthesia, ataxia, dysarthria, deafness, constriction of the visual field, and muscular weakness (Ninomiya et al., 1995; WHO/IPCS, 1990a). Many animal and epidemiological studies indicated that exposure to MeHg can produce delayed neurotoxicity largely characterized by abnormalities in motor function and impairment in visual, auditory, and somatosensory systems (Rice et al., 1999; Rice and Rice, 1996; Tsubaki and Irukayama, 1977; WHO/IPCS, 1989, 1990b).

A cross-sectional study (Yokoo et al., 2003) reported the association between neuropsychological testing and mercury concentrations in the hair of adults living in fishing communities in the Pantanal region of Brazil. This study suggests that adults exposed to low-level MeHg may be at risk for deficits in neurocognitive function such as attention, fine-motor function, and verbal memory. Another study (Weil et al., 2005) determined the effect of low-level mercury exposure on neurobehavior in 474 randomly selected participants in Baltimore City. However, the data did not provide any evidence of an association between blood mercury levels and neurobehavioral performance. In addition, as a normal brain ages, it loses neurons in certain regions as well as neurotransmitter levels and repair mechanisms. Although the possibility of an interaction between aging and exposure to neurotoxic agents was postulated in animal study almost three decades ago (Weiss, 1990; Weiss and Simon, 1975), little is known about high-level mercury exposure and its corresponding formal neuropsychological effects on aging adults.

Abbreviations: T-Hg, total mercury; MeHg, methylmercury; CASI C-2.0, Cognitive Abilities Screening Instrument Chinese version; MMSE, Mini-Mental State Examination; H-MeHg, high-MeHg; L-MeHg, low-MeHg

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From 1942 to 1982, a now-deserted chloralkali plant, between Hsien-Gong Li and Lu-Erh Li, two small administrative units about 18 km from the center of Tainan City, the fourth-largest city in Taiwan, manufactured caustic soda, hydrochloric acid, and liquid chlorine. Chloralkali electrolysis was used to manufacture these products. In this method, mercury is used for electrodes, and chlorine (Cl_2) is produced at the positive electrode (anode), and caustic soda (NaOH), and hydrogen (H_2) are produced, directly or indirectly, at the negative electrode (cathode). During the manufacturing process, a great deal of mercury-contaminated sludge and wastewater were discharged into the nearby ecosystem and then methylated and bio-accumulated in aquatic organisms (Akagi et al., 1979; Imura et al., 1971). Today, therefore, evaluating the blood MeHg levels of people who live along the polluted Lu-Erh Men River and are exposed to mercury is a major concern, because they eat local fish and seafood.

Preliminary surveys by the Taiwan EPA in 1983 and 2004 showed that the mercury levels of fish collected from the Lu Erh Men River (ND—6.9 mg/kg wet weight) and sea reservoir (0.5–3.1 mg/kg wet weight) near the deserted factory were seriously contaminated and would be considered unsafe for human consumption in many countries (UNEP, 2003). Because the local residents usually catch fish and seafood to eat from this watershed (Lee et al., 2006), they may have had a high risk of exposure to MeHg. We therefore hypothesized that the current residents of the area around the deserted chloralkali plant would have higher blood MeHg levels. The aim of this study was to test this hypothesis by determining the blood MeHg levels of the inhabitants living in the neighborhoods around the plant and assessing the association between their blood MeHg levels and cognitive function.

2. Materials and methods

2.1. Participant selection and blood collection

We did this cross-sectional study in July and August 2005 in a local governmental clinic near the deserted chloralkali factory to ensure variability by socioeconomic status and ethnicity. The eligibility requirements were that the participants had to volunteer, had to be between 36 and 70 years old, and had to have lived in the targeted neighborhood (Hsien-Gong Li, Lu-Erh Li, Ssu-Tsao Li, and Yen-Tien Li, four small municipal administrative units) for at least 5 years. We used a two-stage method to reduce the cost and time of sampling. In the first-stage, 526 residents were randomly recruited and blood samples were collected for a total mercury (T-Hg) analysis. All the participants were divided into high- and low-Hg groups by the 75th percentile of total blood Hg levels (19.2 μg/L). Then, the members of the high- and low-Hg groups (1:1 ratio) were invited to join the secondary stage sampling for blood MeHg analysis and Cognitive Abilities Screening Instrument (CASI) cognitive function tests. We finally recruited 252 potential participants: 157 (79%) who had been on the originally invited list and 95 who had volunteered on-site. Apparent alcoholics and individuals with previous traumatic brain injuries or apparent signs of dementia were excluded. After they had signed an informed consent form approved by the Human Ethics Committee of the National Cheng Kung University Hospital, each participant provided 20 mL of venous blood. Blood samples were drawn into chemically clean tubes containing heparin, and were stored at 4 °C until they were analyzed. Information obtained from the questionnaire included personal characteristics (age, gender, medical history, etc.), and lifestyle habits (viz., alcohol intake, tobacco use, and eating habits). Finally, all the participants were given the MMSE (Folstein et al., 1975) and CASI C-2.0 (Liu et al., 2002; Teng et al., 1994) by trained technicians blinded to their blood-mercury levels and dietary history. The researchers measured T-Hg and MeHg levels in blood samples from the participants and then examined their associations with neurobehavioral test scores.

2.2. Measuring total blood mercury

Total blood mercury was measured using automatic heat-vaporization mercury measuring equipment (MA-2000; Nippon Instruments Corporation, Tokyo, Japan) according to the manufacturer's protocol.

2.3. Measuring blood methylmercury

We measured blood MeHg using a previously described method (Vázquez et al., 1999), but with minor modifications. Briefly, 2.5 mL blood was placed in a Teflon-lined tube, and then toluene (15 mL) was added. The extraction was done at a fixed temperature (100 °C) at 100% power in a laboratory microwave extraction system (Microwave Accelerated Reaction System (MARS); CEM Corp., Matthews, NC). After the extraction had been completed and cooled to room temperature, the supernatant of the extracts was transferred into a Teflon tube. The extract was cleaned up using complexation of the MeHg with 3 mL of a 1% aqueous solution of cysteine acetate. Finally, 1 μL of the toluene extract dried over anhydrous sodium sulfate was analyzed using a gas chromatograph (Hewlett-Packard 6890; Hewlett-Packard Company, Palo Alto, CA) equipped with an electron capture detector and an Ulbon HR-thermon-Hg capillary column (15 m long × 0.53 mm internal diameter) (Shinwa Chemical Industries Ltd., Kyoto, Japan).

2.4. Measuring quality control and quality assurance for total mercury and methylmercury

Each analytical run consisted of a method blank, a quality control, and six unknown samples for quality assurance and quality control. Moreover, data quality assurance was monitored by spiking known amounts of T-Hg and MeHg into blood samples and subsequently carrying out the same procedure as is described above. The recoveries of T-Hg and MeHg were 97.9% (76.7–129.6%) and 99.6% (86.2–113.0%), respectively. One blood sample in every batch was analyzed in duplicate; the relative percentage differences of T-Hg and MeHg were 6.6% (0.1–18.8%) and 2.8% (0.0–9.8%), respectively. A reference material, Standard Reference Materials 966, (National Institute of Standards Technology (NIST), Gaithersburg, MD) was also used for quality assurance of T-Hg; the measured concentration (30.6 μg/L) met the certified values (29.7–33.1 μg/L). The method detection limits (MDL) of T-Hg and MeHg were 0.09 and 0.144 μg/L, respectively.

2.5. The Cognitive Abilities Screening Instrument (CASI)

The CASI is globally recognized as a measuring instrument of cognition in epidemiological studies done in the US, Japan, and Taiwan (Liu et al., 2002; Teng et al., 1994). The CASI quantitatively (score range: 0–100) assesses nine cognitive domains: remote memory, recent memory, attention, mental manipulation, orientation, abstract thinking, language, drawing, and verbal fluency. Some of the CASI items are comparable to the items on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Therefore, a CASI-estimated MMSE score (MMSE) was also obtained. Because the CASI is a short, practical test designed to serve multiple functions, it seems to fit well in an extensively mercury-contaminated area. It can be used (a) as a screening instrument for dementia, (b) to monitor disease progression, and (c) to provide a profile of impairment in various cognitive domains. Well-trained interviewers administered the CASI test according to standard operating procedures reported elsewhere (Pai and Chan, 2001).

2.6. Interviewer-administered demographic and dietary questionnaires

Information obtained from the questionnaires included personal characteristics (e.g., gender, age, height, weight, occupational history, and tooth-filling frequency), lifestyle (current alcohol intake and tobacco usage), medical history (including history of neurological diseases such as migraine, polyneuropathy, epilepsy, and Parkinson's disease), and the quantity of dietary intake for the previous 1 year based on a semi-quantitative dietary questionnaire. Questions about the frequency of seafood and fish consumption, with an emphasis on the most frequently consumed marine fish and freshwater fish species and other types of seafood meals, were also included.

The consumption information was calculated based on estimated intake frequencies: 3 times per day, 1–2 times per day, 3–6 times per week, 1–2 times per week, 1–3 times per month, 1–11 times per year, and never (Koppen et al., 2002). Consumption quantity per meal for each type of food was also estimated based on 200-mL bowls for each food item. Trained interviewers administered the questionnaires according to standard operating procedures prepared in advance.

2.7. Statistical analysis

Mercury and MeHg concentrations are reported as μg/L. MS Excel for Windows (MS Office XP) was used for data management, and JMP (version 5.0; SAS Institute, Cary, NC) was used for statistical analysis. The population was divided into high- and low-MeHg (H-MeHg, L-MeHg) groups using 19.2 μg/L (the 75th percentile of blood MeHg level) as the dividing point (H-MeHg: 26.4 ± 10.0 μg/L; $n = 60$; L-MeHg: 11.6 ± 5.0 μg/L; $n = 180$). To control for confounding factors that may have influenced the measurement of MMSE and CASI C-2.0 cognitive function tests, age, gender, and education were matched between the H-MeHg (H-MeHg: 27.0 ± 10.4 μg/L; $n = 46$) and L-MeHg (L-MeHg: 11.6 ± 4.7 μg/L; $n = 92$) groups.