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Neurological and neuropsychological functions in adults with a history of developmental arsenic poisoning from contaminated milk powder

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ABSTRACT

During the summer of 1955, mass arsenic poisoning of bottle-fed infants occurred in the western part of Japan due to contaminated milk powder, and more than 100 died; some childhood victims were later found to suffer from neurological sequelae in adolescence. This unique incident enabled us to explore infancy as a critical period of arsenic exposure in regard to developmental neurotoxicity and its possible persistence through adulthood. The purpose of this work is to evaluate the association between developmental arsenic exposure and the neurological outcomes more than 50 years later. We conducted a retrospective cohort study during the period from April 2012 to February 2013 in two hospitals in Okayama Prefecture, Japan. The study sample consisted of 50 individuals: 27 known poisoning victims from Okayama Prefecture, and 23 non-exposed local controls of similar age. In addition to neurological examination, we adapted a battery of neurophysiological and neuropsychological tests to identify the types of brain functions affected by early-life arsenic exposure. While limited abnormalities were found in the neurophysiological tests, neuropsychological deficits were observed. Except for Finger tapping, all test scores in the exposed group – Vocabulary and Block Design from Wechsler Adults Intelligent Scale III, Design memory subtest from Wide Range Assessment of Memory and Learning 2, and Grooved pegboard test – were substantially below those obtained by the unexposed. The exposed group showed average performance at least 1.2 standard deviations below the average for the controls. Exposed participants performed less well than controls, even after exclusion of subjects with recognized disabilities or those with a high level of education. Adults who had suffered arsenic poisoning during infancy revealed neuropsychological dysfunctions, even among those subjects not recognized as having disabilities. Developmental neurotoxicity due to arsenic likely results in permanent changes in brain functions.

1. Introduction

Chronic exposure to inorganic arsenic via inhalation or drinking-water ingestion has been convincingly linked to lung, skin, and urinary bladder cancer (Straif et al., 2009). In addition, arsenic is known to cause neurotoxicity (National Research Council (U.S.), 1999), and recent studies suggest that early-life exposure to arsenic can cause developmental neurotoxicity (Smith and Steinmaus, 2009; Tolins et al., 2014; Vahter, 2008). However, most previous studies were cross-sectional (Rosado et al., 2007; Tsai et al., 2003; Vibol et al., 2015; von Ehrenstein et al., 2007; Wang et al., 2007; Wasserman et al., 2014; Wasserman et al., 2007; Wasserman et al., 2004; Wright et al., 2006) and only a few studies were longitudinal (Hamadani et al., 2010; Hamadani et al., 2011; Tofail et al., 2009), thus leaving the relation of adverse effects to the timing of exposure uncertain. Therefore, little is known about the possible variation in susceptibility depending on age, i.e., the critical period of exposure.

During the summer of 1955, mass arsenic poisoning of bottle-fed infants occurred in the western part of Japan due to contaminated milk powder that resulted in an estimated arsenic concentration in the reconstituted milk of about 4–7 mg/L (Dakeishi et al., 2006; Hamamoto, 1957). The contaminated milk was announced as the cause of the poisoning cases and was recalled on August 24th, 1955.

Abbreviations: BAEP, brainstem auditory evoked potential; NCV, nerve conduction velocity; VEP, visual evoked potential; WRAML2, Wide Range Assessment of Memory and Learning 2; WAIS-III, Wechsler Adults Intelligence Scale III.

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At that point, exposures had lasted for at least four months since the change in formulation of the milk powder in April 1955 (Hamamoto, 1957). Approximately 13,000 Japanese children were affected, and most cases occurred in the western part of the country where the factory was located (Hikari Association, 2015). Affected infants manifested skin pigmentation, diarrhea, and fever, and more than 100 died from acute poisoning (Hamamoto, 1957). Subsequent studies showed that adolescents exposed as infants to the contaminated milk powder had a lower IQ than the general population (Ohira and Aoyama, 1973; Yamashita et al., 1972).

This unique incident of arsenic exposure enables us to explore infancy as a critical period of arsenic exposure in regard to developmental neurotoxicity persisting through adulthood. Therefore, we aimed to evaluate the association between developmental arsenic exposure from contaminated milk powder and the neurological, neurophysiological, and neuropsychological outcomes more than 50 years later. The overall purpose was to identify the types of brain functions primarily affected by early-life arsenic exposure.

2. Methods

2.1. Study setting

We conducted a retrospective cohort study during the period from April 2012 to February 2013 at two hospitals (Okayama Kyoritsu Hospital and Mizushima Kyodo Hospital) in Okayama Prefecture, Japan. We targeted Okayama Prefecture because this Prefecture was the most severely affected area in the country (Hamamoto, 1957). We determined neurological, neurophysiological, and neuropsychological outcomes as well as demographic characteristics using questionnaires in connection with the participants' regular health examinations. All examiners were blinded as to the participants' exposure status.

2.2. Study participants

The study sample consisted of 50 individuals who provided written, informed consent for participation in the study: 27 among known poisoned victims in Okayama Prefecture and 23 local, non-exposed controls. Among those invited, three exposed and three non-exposed individuals refused to participate in the study. The exposed participants were identified from a list of victims known to the Hikari Association to receive free health care at the two hospitals ($n = 15$). The Hikari Association is a public-interest foundation dedicated to provide permanent relief for the victims of the contaminated milk powder. It supports victims through various efforts, such as benefits, including living allowance, and regular health examinations for those who have disabilities or a relevant medical diagnosis. According to the Hikari Association, it supports regular health examinations for victims with disorders specific to arsenic poisoning, such as intellectual disability, mental disorder, or skin lesions. Among the 15 participants identified through the Association, 12 received benefits for their disorders, while three participants did not receive any, because they did not suffer from qualifying disorders. The list of exposed participants was supplemented by a list of victims who did not receive regular health examinations offered by the Hikari Association but who could be reached through the two local hospitals ($n = 12$); the hospitals offered health care to these victims regardless of their current health status. Thirteen exposed participants were born in 1954 and were at least five months old when the contamination started, while 14 were born in 1955 and would therefore have been exposed at a younger age before the official warning against the milk powder was issued in August of 1955. No information could be retrieved about the duration of breast-feeding. We recruited 23 non-exposed controls from the medical staff, including clerks, nurses, laboratory technicians, and one physician at the two hospitals, at ages similar to the exposed participants. None of them had been exposed to the contaminated milk powder during infancy.

2.3. Neurological tests

One neurologist employed at each of the two hospitals conducted all clinical neurological examinations. They performed a screening-type neurological examination including mental status (e.g., level of consciousness, speech and language, memory, agnosia, and apraxia), cranial nerves, motor system (e.g., visual inspection, tone, and strength), sensory system (e.g., touch, pain, vibration, and joint position sense), reflexes, coordination (e.g., finger-nose-finger), and gait. They also asked the participants about symptoms related to autonomic function (e.g., genitourinary retention, incontinence, constipation, and diarrhea) and checked for orthostatic hypotension. Based on these results, they provided summary scores with regard to mental, motor, sensory, and autonomic functions being normal or abnormal.

2.4. Neurophysiological tests

All of the neurophysiological tests [Nerve conduction velocity (NCV), brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs)] were conducted in the hospitals using standardized methods and the same instrumentation (Neuropack S1, Nihon Kohden). We calculated motor NCV of the median nerve in both hands. We performed BAEPs and VEPs on both sides and used the averages for statistical analyses. Because VEP assessment was not possible in one hospital (Okayama Kyoritsu Hospital), only the 23 participants at the other hospital were tested. Although pattern-reversal VEPs may be preferable because of their better specificity, we used flash VEPs due to its availability as routine procedure.

2.5. Neuropsychological tests

One psychologist (TK) administered all of the neuropsychological tests to all participants. The tests took about half an hour on average, although exposed subjects generally took longer than the controls.

2.5.1. Two subtests (Vocabulary and Block Design) from Wechsler Adults Intelligent Scale III (WAIS-III)

WAIS-III is a test for measuring intelligence in adults and contains 14 subtests. Out of those, we selected two (Vocabulary and Block Design). With regard to Vocabulary, words of increasing difficulty were presented to the participants both orally and visually, and they were asked to define the words. This component measures verbal knowledge and concept formation. With regard to Block Design, the participants were asked to arrange the blocks to match the design formed by the examiner or shown on cards. This component measures spatial problem-solving and manipulative abilities. We then calculated standardized scores of both components.

2.5.2. Design memory subtest from Wide Range Assessment of Memory and Learning 2 (WRAML2)

WRAML2 measures learning and memory functions and is composed of six core subtests. We selected design memory subtest among them. The participants viewed each card for five seconds, and then after a ten-second delay the participants were asked to draw what they remembered. The participants repeated the task five times for five stimulus cards. The subtest measures reproduction from visual memory.

2.5.3. Grooved pegboard test

Grooved pegboard is a dexterity test to measure complex visual-motor coordination. We used the Grooved Pegboard (Model 32025, Lafayette Instrument Company, USA), which consists of 25 holes with randomly positioned slots. The participants were asked to rotate pegs, which have a key along one side, to match the hole. The participants performed the test with both dominant and non-dominant hands. We recorded the duration (in seconds) required to perform each trial,