Neurotoxicology and Teratology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Association of lifetime exposure to fluoride and cognitive functions in Chinese children: A pilot study

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A R T I C L E I N F O

Article history:
Received 27 May 2014
Received in revised form 9 October 2014
Accepted 3 November 2014
Available online xxxx

Keywords:
Children
Confounding
Fluoride
Fluorosis
Neuropsychological measures
Prenatal exposure delayed effects

A B S T R A C T

Background: A systematic review and meta-analysis of published studies on developmental fluoride neurotoxicity support the hypothesis that exposure to elevated concentrations of fluoride in water is neurotoxic during development.

Methods: We carried out a pilot study of 51 first-grade children in southern Sichuan, China, using the fluoride concentration in morning urine after an exposure-free night; fluoride in well-water source; and dental fluorosis status as indices of past fluoride exposure. We administered a battery of age-appropriate, relatively culture-independent tests that reflect different functional domains: the Wide Range Assessment of Memory and Learning (WRAML), Wechsler Intelligence Scale for Children-Revised (WISC-R) digit span and block design; finger tapping and grooved pegboard. Confounder-adjusted associations between exposure indicators and test scores were assessed using multiple regression models.

Results: Dental fluorosis score was the exposure indicator that had the strongest association with the outcome deficits, and the WISC-R digit span subtest appeared to be the most sensitive outcome, where moderate and severe fluorosis was associated with a digit span total score difference of −4.28 (95% CI −8.22, −0.33) and backward score with −2.13 (95% CI −4.24, −0.02).

Conclusions: This pilot study in a community with stable lifetime fluoride exposures supports the notion that fluoride in drinking water may produce developmental neurotoxicity, and that the dose-dependence underlying this relationship needs to be characterized in detail.

1. Introduction

The developing human brain is much more susceptible to injury caused by toxicants than is the mature brain, and the damage incurred is likely to be of a permanent nature as the major windows of developmental vulnerability occur in utero and during infancy and early childhood (Grandjean and Landrigan, 2006; Rice and Barone, 2000). Chemicals can, therefore, cause permanent brain injury at low levels of exposure that would have little or no adverse effect in an adult (Grandjean and Landrigan, 2014).

Fluoride occurs naturally in the environment from the weathering of fluoride-containing rocks and soils, and leaching from soil into groundwater. Fluoride is also released into the environment via coal combustion and other industrial sources, either by direct deposition or by deposition to soil and subsequent runoff into water (NRC, 2006; WHO, 2002). The major sources of human exposure to fluoride are drinking water, food, dental products, and pesticides (NRC, 2006). Fluoride is a trace element that is necessary for the human body. A proper amount of fluoride not only prevents dental caries, but also promotes the use of calcium and phosphorus and the calcium sediment in the bone, stimulates bone growth and maintains bone health (Dean and Elvove, 1936; WHO, 1958).

However, the developing human brain may be exposed prenatally to fluoride as fluoride readily crosses the placenta (ATSDR, 2003). In laboratory studies, the central nervous system (CNS) may be vulnerable to fluoride. Fluoride accumulates in brain tissues and may affect the hippocampus, the central processor of memory, in learning and memory

Abbreviations: CDC, Center for Disease Control; SD, standard deviation.

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http://dx.doi.org/10.1016/j.ntt.2014.11.001

functions (Mullenix et al., 1995; Chioca et al., 2008). Potential effects on the neurodevelopment in children have been explored mainly in China where many urban and rural communities are located in endemic fluorosis areas. Thus, a National Research Council report reviewed the effects of fluoride in drinking water on human health, including the cognitive capacities in children (NRC, 2006). Many relevant studies were identified that, collectively, supported the hypothesis that fluoride is a developmental neurotoxicant, but because many of the studies did not provide sufficient information about the neurobehavioral tests used and the testing conditions, the report recommended that additional, more rigorous research be conducted.

In response to this report, the U.S. Department of Health and Human Services (DHHS) is proposing to set the recommended level of fluoride in drinking water at 0.7 mg/L, the lower end of the current range of 0.7 to 1.2 mg/L, and the U.S. Environmental Protection Agency (U.S. EPA) is considering lowering the maximum amount of fluoride allowed in drinking water, which is currently 4 mg/L (U.S. EPA, 2011).

To investigate the effects of increased fluoride exposure on children's neurobehavioral development, we performed a systematic review and meta-analysis of 27 cross-sectional studies of children exposed to fluoride in drinking water, mainly from China (Choi et al., 2012). Our results showed that the standardized weighted mean difference (SMD) in IQ score between exposed and reference populations across studies that gave the average difference in standard deviations (SDs) was −0.45 (95% confidence interval: −0.56, −0.36). For commonly used IQ scores with a mean of 100 and a SD of 15, 0.45 SDs is equivalent to 6.75 points (rounded to 7 points). The results therefore showed an average IQ decrement of about seven points in children with increased fluoride exposure. The elevated exposure groups had access to drinking water with fluoride concentrations ranging from 0.57 mg/L to 11.5 mg/L. As the average difference in terms of IQ between elevated and background exposure groups corresponded to approximately 7 points, our review highlighted a need to further characterize the dose–response association including improving assessment and control of potential confounders.

The current pilot study was undertaken to assess the feasibility of administering a comprehensive battery of neurodevelopmental tests to a population of school children in China in order to test the hypothesis that increased fluoride exposure is related to impairments in neurobehavioral development. Specifically, we identified a population of children who had been exposed to stable fluoride concentrations in drinking water since conception and assessed the feasibility and validity of exposure assessment and neurobehavioral testing under field conditions in rural China. In this country, a country-wide effort to provide microbiologically safe drinking-water in rural communities secured piped spring water or well-water for each household. Families residing at the same location could therefore be characterized in regard to fluoride exposure based on the concentration of fluoride in a child's water source.

2. Materials and methods

2.1. Study population

We carried out a field study of 51 first-grade children, aged 6–8 years in 2011, who resided in Mianning County in southern Sichuan, China. While there is a wide range of fluoride concentrations in drinking water in this area, the residence-specific water sources have very stable fluoride levels. For families remaining at the same residence, the children have therefore been exposed to a stable fluoride concentration since conception. Children who did not speak Chinese, who were not students at the Primary School of Sunshui Village in Mianning County, or who had a chronic or acute disease that might affect neurobehavioral function tests were excluded.

The study protocol was approved by the Ethics Committee of China Medical University and by the Institutional Review Board at the Harvard School of Public Health. Written informed consent was obtained from all parents or guardians.

2.2. Measurements of exposure

Fluoride concentrations in well-water in the communities were measured and recorded by Mianning County Center for Disease Control (CDC). Apart from seasonal changes, the well-water fluoride concentrations have remained the same over the years, and the residents generally consistently use the same source for their drinking water needs. Well-water fluoride concentrations of the mother's residence during pregnancy and onwards were therefore used to characterize a child's lifetime exposure. Review of CDC records documented that levels of other contaminants, including arsenic and lead, are very low in the area.

Due to the stable residence of the study population, current exposures are thought to be representative of chronic exposures. Additionally, the urinary fluoride excretion after an exposure-free night was used as a reflection of the release from skeletal deposits of fluoride. To provide a measure of the accumulated body burden, each child was therefore given a 330 mL (11.2 oz) bottle of Robust© distilled water (free from fluoride and other contaminants) to drink the night before the clinical examinations, after emptying the bladder and before bedtime. The parents or guardians were instructed to ensure that the child would only drink the distilled water during this period and that the child did not have other sources of water prior to the study visit day. The first urine sample the following morning was collected at home, and the fluoride concentration was determined on a 5 mL sample using an ion-specific electrode (Whitford, 1996) at the Mianning Center for Disease Control (CDC).

One of the investigators (YZ), a dentist, performed a blinded dental examination on each child's permanent teeth to rate the degree of dental fluorosis using the Dean Index (Dean, 1942; WHO, 1997). Dental fluorosis is caused by excess fluoride exposure when the teeth are being formed. The Dean Index is a commonly used index in epidemiological studies and remains the gold standard in the dentistry armamentarium. The Index has the following classifications: normal, questionable, very mild, mild, moderate, and severe. The severity of the condition depends on the dose, duration, and the timing of fluoride intake. Questionable fluorosis indicates teeth with a few white flecks or spots. It is sometimes difficult to draw a clear distinction between the Questionable from the Normal. Very mild and mild forms of dental fluorosis indicate that teeth have scattered white flecks, occasional white spots, frosty edges, or fine and lacy chalk-like lines. Moderate and severe forms of dental fluorosis indicate that teeth have larger white spots and in the rare and severe forms, rough and pitted surfaces.

The well-water fluoride concentrations of the residence during pregnancy and onwards, the fluoride concentration in a child's first urine sample in the morning, and the degree of the child's dental fluorosis were used as indicators of exposure to fluoride.

A 20 μL capillary blood sample was collected at the school by a Mianning CDC health practitioner and tested for possible iron deficiency which could be used as a covariate of neurodevelopmental performance.

2.3. Outcome measurements

We adopted culture-independent tests considered feasible for children aged 6 to 8 years, and reflecting a variety of functional domains. The selection was based on several considerations. The very sparse literature on fluoride neurotoxicity does not provide strong clues as to what domains would be expected to be most affected. To date, studies have predominantly reported only on IQ scores (and often only on scores yielded by tests such as the Raven Progressive Matrices test, which assesses a limited range of relevant functions). Therefore, we decided to use tests that assess various important domains, using those that we have found to be useful in other studies we have conducted in non-English speaking, rural populations, such as the Amazon and