The Developmental Neurotoxicity of Arsenic: Cognitive and Behavioral Consequences of Early Life Exposure

Molly Tolins, MD, Mathuros Ruchirawat, PhD, and Philip Landrigan, MD, MSc

ABSTRACT

Background: More than 200 million people worldwide are chronically exposed to arsenic. Arsenic is a known human carcinogen, and its carcinogenic and systemic toxicity have been extensively studied. By contrast, the developmental neurotoxicity of arsenic has been less well described. The aim of this review was to provide a comprehensive review of the developmental neurotoxicity of arsenic.

Methods: We reviewed the published epidemiological and toxicological literature on the developmental neurotoxicity of arsenic.

Results: Arsenic is able to gain access to the developing brain and cause neurotoxic effects. Animal models link prenatal and early postnatal exposure to reduction in brain weight, reductions in numbers of glia and neurons, and alterations in neurotransmitter systems. Animal and in vitro studies both suggest that oxidative stress may be a mechanism of arsenic neurotoxicity. Fifteen epidemiological studies indicate that early life exposure is associated with deficits in intelligence and memory. These effects may occur at levels of exposure below current safety guidelines, and some neurocognitive consequences may become manifest only later in life. Sex, concomitant exposures, and timing of exposure appear to modify the developmental neurotoxicity of arsenic. Four epidemiological studies failed to show behavioral outcomes of arsenic exposure.

Conclusions: The published literature indicates that arsenic is a human developmental neurotoxicant. Ongoing and future prospective birth cohort studies will allow more precise definition of the developmental consequences of arsenic exposure in early life.

Key Words: arsenic, behavioral effects, children's environmental health, cognition, developmental neurotoxicity, developmental origins of adult disease

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INTRODUCTION

The World Health Organization (WHO) estimates that more 200 million people worldwide are chronically exposed to arsenic at levels above proposed safety standards.[1] Contaminated ground water is the principal route of exposure, but airborne exposures make additional contributions, especially in the vicinity of mines, smelters, and industrial "hot spots."

Contaminated drinking water is the main route of human exposure to arsenic. Widespread contamination of ground water by arsenic has been reported in Bangladesh, West Bengal, China, Taiwan, Thailand, Ghana, Argentina, Chile, Mexico, Hungary, Canada, the United Kingdom, and areas of the United States.[2] Its presence in the environment can be a result of natural sources, such as erosion or geological leaching, or anthropogenic sources, including mining, industrial wastes, and use of fertilizers containing arsenic.

Other less common sources of arsenic exposure include coal combustion and incineration of arsenic-preserved wood products. Consumption of tainted foods, ingestion of kitchen dust, inhalation of indoor air polluted by coal combustion, tobacco smoke, and hand-to-mouth soil ingestion have been reported as additional routes of arsenic exposure.[2,3] Airborne exposures, especially in the vicinity of mines, smelters, and industrial "hot spots," make further contributions.

Arsenic has been shown to cross the placenta, and studies have also shown that in utero exposure may occur. One study used arsenic-labeled arsenate and arsenite in pregnant mice and by using autoradiography

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From the Laboratory of Environmental Toxicology, Chulabhorn Research Institute, Laksi, Bangkok, Thailand (MT, MR); Departments of Preventive Medicine and Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY (MT, PL). Address correspondence to: (M.T.); e-mail: molly.tolins@mssm.edu

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and gamma counting, observed that the arsenic passed through the placenta from the maternal to the fetal circulation.[4] Other studies have also shown transplacental arsenic transfer in animal models.[5,6] Similar findings have been described in humans. Strong positive correlations have been found between cord and maternal blood arsenic levels in arsenic-exposed pregnant women,[7] and it has been demonstrated that levels of arsenic in cord and maternal blood were nearly identical among pregnant women living in an arsenic-contaminated area, suggesting virtually free passage of arsenic across the placenta from the mother to the fetus.[8] Individual arsenic metabolites have been found to be strongly correlated in cord and maternal blood (inclusive of dimethylarsinate, monomethylarsonate, arsenite, and arsenate).[7] These findings suggest the developing fetus is at risk for arsenic exposure via placental transfer.

Breast milk is another potential route of exposure for young children. However, animal studies have failed to show arsenic in breast milk. In a study of low-dose drinking water arsenic exposure, no arsenic was measured in the breast milk of exposed mice.[9] It has been demonstrated that arsenic does not appear to pass into human breast milk, and thus was hypothesized that breast-feeding may therefore protect against arsenic exposure in Bangladeshi infants.[10]

Once arsenic gains access to the neonate, however, it may cross the blood—brain barrier (BBB) and directly affect the central nervous system (CNS). The BBB is a structure composed of tight junctions between capillary endothelial cells in the brain and epithelial cells in the choroid plexus specialized to prevent proteins and smaller molecules from mixing with the cerebrospinal fluid.[11] The neurotoxicity of a toxicant therefore depends in part on the permeability of the BBB to that toxin.[12] In the case of arsenic, animal studies have shown that brain arsenic levels have a dose—response relationship to levels of arsenic in drinking water, demonstrating that the BBB does not effectively block the passage of arsenic to the CNS.[12-16] Additionally, it has been reported that arsenic may have a direct toxic impact on the BBB itself. A study on the effects of mixed metals on the BBB,[12] showed that various metals, arsenic among them, disrupted the integrity of the BBB likely via effects on astrocytes, leading to increased permeability of the BBB to toxicants such as arsenic.

Exposure Guidelines and Effects on Health

Major scientific reviews of arsenic toxicity by the National Academy of Sciences, the National Drinking Water Advisory Council, and the U.S. Environmental Protection Agency's (EPA) Science Advisory Board have confirmed that arsenic can have negative effects on human health at lower levels than previously suspected. These findings led the EPA to reduce the acceptable level of arsenic in drinking water from 50 to 10 μg/L. Health Canada has proposed that the maximum acceptable concentration for arsenic in drinking water in Canada should be 5 μg/L, and as an interim measure has lowered its guidelines from 50 to 25 μg/L while technologies are developed to further reduce arsenic in drinking water.[2,17] Similarly, the WHO has stated that the guideline for arsenic in drinking water would be 0.17 μg/L based on acceptable excess lifetime cancer risk of 10^{-5}, but as this value is below the practical quantification limit, 10 μg/L was accepted as the provisional guideline value.[18]

The health effects of chronic, low-level exposure to arsenic include skin pigmentation, hypertension, cardiovascular disease, diabetes, anemia, reproductive effects, developmental effects, immunologic effects, and neurological disorders.[2,18,19,20] Arsenic is also a carcinogen.[21] The International Agency for Research on Cancer (IARC) considers arsenic a proven human carcinogen that definitely causes cancers of the lung, urinary bladder, and skin and additionally is linked to cancers of the kidney, liver, and prostate.[22] Infants and children appear to be especially vulnerable to these effects, likely because of their greater consumption of food and drinking water on a body-weight basis than adults.[23]

Although the systemic and carcinogenic toxicities of arsenic have been studied in detail, its neurocognitive consequences have not been extensively explored. The aim of this review was to evaluate and synthesize the findings of the available epidemiological, animal, and in vitro studies on the intellectual and behavioral effects of chronic arsenic exposure, especially of exposures in early life.

METHODS

A literature review was performed, using PubMed, library catalogues, and journals available at the Icahn School of Medicine at Mount Sinai Levy Library. These sources were searched using key words such as: arsenic or arsenic* and intellectual, cognitive, neuro*, neurotox*, intelligence, neurol*, IQ, behavior*, neurobehavior*. All types of relevant animal, in vitro, and human studies were considered including journal articles, reports, and book chapters, with an emphasis on more recent and more robust studies, and a focus on early life and prenatal arsenic exposure. Articles not written in English were excluded.

Studies Included

Ultimately, 47 papers were included in this review, made up of animal studies, in vitro studies using animal tissues, in vitro studies using human tissues, epidemiological studies, and meta-analyses. These 47 papers included only those used to address the question of the neurotoxic effects of arsenic, and did not include those cited as part of the introduction or as background citations in the body of the manuscript not directly related to the focus of this review (see Table 1 for studies included by type).