Drinking water arsenic exposure, thyroid hormone biomarkers and neurobehavioral outcomes in adolescents

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ABSTRACT: Exposure to arsenic (As) from drinking water has been linked to neurocognitive impairment, however, the physiological mechanisms of As-induced neurotoxicity are not known. Emerging evidence from animal studies suggest disruption of the endocrine system in early life as a plausible mechanism. We examined neurobehavioral performance and serum thyroid hormone (TH) among adolescents living in Arai-hazar, Bangladesh who have been consistently exposed to water arsenic (WAs) above and below $10 \mu\text{g L}^{-1}$ since *in utero*. Mothers of these children are participants of the Health Effects of Arsenic Longitudinal Study (HEALS). We have observed inverse relationships between As exposure and TH biomarkers as well as between TH and multiple neurobehavioral outcomes in these adolescents. Findings from this study suggest that As-induced neurotoxicity may be mediated via disruption of thyroid hormone.

1 INTRODUCTION

Chronic arsenic (As) exposure has been recognized as a major environmental health problem that affects multiple organs and biological systems including the developing brain in children (Das *et al.*, 2012; Gong *et al.*, 2015; Wasserman *et al.*, 2007). Thyroid hormones (TH), on the other hand, are key determinants of the development and maturation of central nervous system (CNS) from the pre-natal period to the middle of childhood (Brent, 2010; Gilbert *et al.*, 2012; Parvez *et al.*, 2011; Rosado *et al.*, 2007; Rovet, 2014; Roy *et al.*, 2011). Therefore, one potential mechanism linking As exposure to neurocognitive function is the disruption of thyroid hormone (TH) action. Arsenic appears to interfere with thyroid function by lowering blood levels of thyroid hormone (Kahn *et al.*, 2014; Wasserman *et al.*, 2014; Zoeller *et al.*, 2014). The goal of the present study was to examine the relationships between water As (WAs), four serum TH biomarkers such as free thyroxine (fT₄), thyroid stimulating hormone (TSH), total triiodothyronine (tT₃) and antibodies to thyroperoxidase (TPOAb) and neurodevelopmental outcomes measured by the Behavioral Assessment and Research System BARS computer test battery in adolescents in Bangladesh who have known WAs exposure history from birth to adolescence.

2 MATERIALS AND METHODS

We recruited 32 healthy adolescents (16 boys and 16 girls) aged between 15 and 17 years whose mothers have been participating in the Health Effects of

Arsenic Longitudinal Study (HEALS), since 2000 in Arai-hazar, Bangladesh. Every mother brings water for all family members and therefore, the sources of drinking water for mother and her child remain the same. Currently, we have WAs and Urinary As (UAs) data available for the mothers covering at least five critical stages of childhood: birth, age 3, 6, 9, and 12, which helped us estimate lifetime WAs exposure. Half of these children were consistently exposed to WAs above the EPA/WHO MCL of $10 \mu\text{g L}^{-1}$ from prenatal to adolescence; the remaining half had consistent low lifetime WAs exposure ($<10 \mu\text{g L}^{-1}$). We analyzed their serum samples for thyroid biomarkers at the IUB Toxicology Laboratory, urine samples for UAs at Trace Metal Core Laboratory of Columbia University and also evaluated their neurobehavioral performance using the Behavioral Assessment and Research System (BARS) test battery. The computer-based tests in BARS measure attention, response speed, coordination and memory by recording time and accuracy of the responses of the participants even if they do not have prior experience in computer use.

3 RESULTS

3.1 Arsenic exposure and thyroid biomarkers

There was no significant difference between high and low As exposed children in terms of age, BMI and blood pressure. We observed that concurrent WAs and UAs were negatively associated with fT₄. At the same time, both WAs and UAs were positively and significantly correlated with TPOAb, which is consistent with earlier reports in adults (Table 1).

Table 1. Spearman correlation coefficients for the relationships between lifetime (In utero and early life) As exposure and serum thyroid biomarkers.

Exposure Variables	Total T ₃	Free T ₄	TSH	TPOAb
Urinary As (μg/g Cr)	0.05	−0.10	0.01	0.43**
Water As (ppb)	0.02	−0.16	−0.06	0.36*

**p-value = 0.015; *p-value = 0.04

Table 2. Spearman correlation coefficients for the associations between serum thyroid biomarkers and NB outcomes.

NB Outcomes	Total T ₃	Free T ₄	TSH	TPOAb
Digit span F	−0.14	0.31	−0.10	−0.19
Digit span R	−0.03	0.21	−0.03	−0.25
Symbol digit latency (ms)	−0.05	−0.13	0.18	0.20
Reaction time latency (ms)	−0.06	0.09	0.41*	0.18
Continuous performance latency (ms)	−0.28	0.38	0.22	0.15
Continuous performance d-prime	−0.34	−0.09	0.12	0.22
Match-to-sample (correct count)	0.23	0.16	−0.36*	0.04
Match-to-sample (correct latency ms)	−0.23	−0.11	0.03	−0.04

Associations demonstrating inverse relationship of serum thyroid biomarkers with NB outcomes are in bold text; *p < 0.05

3.2 Arsenic exposure and NB outcomes

With a shorter form of the BARS test battery containing five tests we demonstrated that children exposed to high WAs had poorer neurobehavioral (NB) performance in six out of eight outcome variables (data not shown). This observation showing a negative impact of As on multiple measures NB performance is consistent with the findings of previous epidemiological studies.

3.3 Thyroid biomarkers and NB outcomes

We examined the correlations between concurrent thyroid function biomarkers and NB outcomes. Significant negative association between TSH and match-to-sample correct count ($p = 0.04$) and significant positive association TSH and reaction time latency ($p = 0.02$) were observed. Majority of the associations of NB outcomes with TH biomarkers are consistent with the hypothesis that increased TSH and TPOAb and decreased tT3 and fT4 predict decline of cognitive functions in adolescents (Table 2).

4 CONCLUSIONS

Overall, our findings demonstrate that thyroid system disruption by WAs can be revealed by decreased free thyroxine (fT4) or total triiodothyronine (tT3) and increased serum thyroid stimulating hormone (TSH) and antibodies to thyroperoxidase (TPOAb) in

adolescents, which in turn may lead to neurocognitive deficits in children.

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