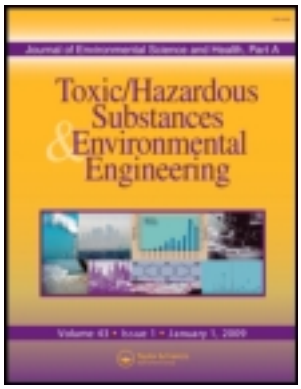

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Debendra Guha Mazumder [a], Ishanikar Purkayastha [a], Aloke Ghose [a], Goutom Mistry [b], Chandan Saha [b], Ashoke K. Nandy [b], Arabinda Das [c] & Kunal K. Majumdar [d]

[a] DNGM Research Foundation, Kolkata, India

[b] Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, India

[c] Department of Statistics, Acharya Prafulla Ch. College, Kolkata, India

[d] Department of Community Medicine, KPC Medical College & Hospital, Jadavpur, Kolkata, India

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Hypertension in chronic arsenic exposure: A case control study in West Bengal

DEBENDRA GUHA MAZUMDER[1], ISHANIKAR PURKAYASTHA[1], ALOKE GHOSE[1], GOUTOM MISTRY[2], CHANDAN SAHA[2], ASHOKE K. NANDY[2], ARABINDA DAS[3] and KUNAL K. MAJUMDAR[4]

[1]*DNGM Research Foundation, Kolkata, India*
[2]*Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, India*
[3]*Department of Statistics, Acharya Prafulla Ch. College, Kolkata, India*
[4]*Department of Community Medicine, KPC Medical College & Hospital, Jadavpur, Kolkata, India*

Various systemic manifestations are reported to be caused by chronic arsenic exposure in the population living in the Indo-Bangladesh subcontinent. This study from West Bengal assesses the likelihood of occurrence of hypertension (HTN) in individuals resident in an area of high groundwater contamination with arsenic (Nadia district) compared to those from a non-contaminated area (Hoogly district) in West Bengal, India. Two hundred and eight study participants (Group 1) were recruited from a cross-sectional study in six villages in the Nadia district and 100 controls (Group 2) from a village in the Hoogly district. The two groups were evenly matched in regard to age and sex. History taking and clinical examination including blood pressure measurement were undertaken in each participant. Water samples from current and previous drinking water sources and hair and urine samples from each participant were collected for estimation of arsenic. The present study shows evidence of increased association of HTN in individuals resident in arsenic endemic region compared to those from a non-endemic region in West Bengal. There were increased odds ratios for HTN [Adjusted Odds Ratio, OR, 2.87 (95 %CI = 1.26–4.83)] in Group- 1 participants compared to Group- 2 people. Within Group 1, there was no difference in prevalence of HTN between those with and without skin lesion. There was a dose-effect relationship seen with increasing cumulative arsenic exposure and arsenic level in hair and HTN in participants living in arsenic endemic region.The findings reported here support an association between arsenic exposure and HTN. More work is needed to characterize the link further.

Keywords: Arsenic and hypertension, Arsenic in hair, Arsenic in unexposed population.

Introduction

Arsenic in drinking water is recognized as a major public health problem in several regions of the world. Major affected regions of South-East Asia region the basin of the Ganga-Brahmaputra-Meghna Rivers and the Mekong Delta.[1, 2] Although since reported across different states in Eastern India, the occurrence of disease resulting from arsenic toxicity was reported in West Bengal as early as 1983.[3] Besides pigmentation and keratosis, arsenicosis produces systemic manifestations including chronic respiratory disease, peripheral neuropathy, liver fibrosis, edema of legs, anemia and cancers.[4, 5, 6, 7, 8] Chronic exposure has also been associated with development of peripheral vascular disease, particularly in Taiwan where drinking of Artesian well water has been linked to Black Foot Disease (BFD).[9,10,11,12] Increased prevalence of hypertension (HTN) and a dose-response relationship with ingested inorganic arsenic have been documented among residents in BFD endemic areas of Taiwan.[13] Hypertension has also been reported in arsenic exposed people in Chile[14] and Bangladesh.[15]

Increased mortality rate from ischemic heart disease HTN and IHD has been reported among residents in BFD endemic regions of Taiwan.[16–18] History of arsenic exposure was estimated through information obtained from the arsenic content in artesian well water of the villages.[19]

However, there is no clear consensus on the causal relationship between arsenic and cardiovascular disease. A systematic review of the epidemiological evidence identified methodological limitations that limited the interpretation of the moderate to strong association between high arsenic exposure and cardiovascular outcomes in Taiwan. In other populations and in occupational settings, the evidence has been inconclusive.[20]

Address correspondence to Debendra Guha Mazumder, Director, DNGM Research Foundation, 37/C, Block 'B', New Alipore, Kolkata 700053, India; E-mail: guhamazumder@yahoo.com
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In this community-based study association of HTN were ascertained on the basis of blood pressure measurement with individual arsenic exposure data in individuals resident in an area of high groundwater contamination with arsenic compared to those from a non-contaminated area in West Bengal, India. A secondary aim was to explore possible dose-response relationships with arsenic and the significance of skin lesions as an indicator of HTN.

Materials and methods

This study determined the prevalence of HTN, across two groups recruited on the basis of likely exposure status of arsenic as determined by area of residence. Group-1 (exposed) was drawn from geographical areas known to have high levels (>50 μg/L) of arsenic contaminated ground water and Group-2 (unexposed) was drawn from an area where groundwater was not contaminated with arsenic [arsenic level in ground water below detection limit (BDL) i.e., <3 μg/L].

Subject selection

Two hundred and eight exposed participants (Group-1) were selected from a population of 900 residents belonging to 212 households (4 % of total households in the selected villages) in six villages in the two blocks, included in a cross-sectional study previously done in ground water arsenic contaminated region of the whole district of Nadia, West Bengal, India.[21] Out of 208 participants of Group-1, 108 arsenicosis cases with arsenical skin lesion and 100 participants without arsenical skin lesion were selected randomly from 191 and 709 subjects with and without such lesion respectively amongst the total 900 subjects of the 212 households of Nadia. The 100 unexposed participants (Group-2) were recruited from one village in the Hoogly district, West Bengal without having arsenic contamination (arsenic level in groundwater <3 μg/L), age- and sex-matched with the participants belonging to Group-1. All subjects included in this study gave written consent for their participation. Approval of the study protocol was obtained from the Ethical committee of the Foundation, fulfilling the Helsinki criteria and recommendation of Indian Council of Medical Research, Govt. of India.

Field study

Information from each recruit was collected on demographic and social characteristics and addiction to smoking, alcohol or chewing tobacco with betel nut. Weight and Height were measured, and Body Mass Index (BMI) was calculated (Weight in Kg/Height in meter^2). All the participants were clinically examined including examination for typical arsenical skin lesion of pigmentation and/or keratosis and recording of blood pressure was done. [8].

Measurement of exposure

All exposed participants were questioned on lifetime history of water consumption using a structured questionnaire. Questions were asked as to sources of drinking and cooking water, and duration of water use from each source. Water samples were collected from present drinking and cooking water source of each participant and also from previous water sources when they were still available, in a polyethylene bottle from participants belonging to both the groups. Cumulative arsenic exposures were calculated for each respondent, using the formula Σ (C_ix D_i) where C_i was the concentration of arsenic in particular well water which a study subject had used during the period i and D_i was the duration of use.

First morning void urine sample was also collected from participants in a container. Both the water and urine samples were kept in ice box before shifting from the field and stored at -20°C. For collection of hair, a bunch of whole length hair sample was cut from the scalp of each participant by a stainless blade and kept in a plastic packet. All these samples were stored according to standard protocol of WHO (2005) until further analysis.[8]

Arsenic levels in urine, hair and water were measured using an atomic absorption spectrophotometer with a flow-injection hydride generation system as described by Das et al (1995).[22] The limit of detection determined at the 90 % confidence level was 3 μg/L. Hair samples were thoroughly cleaned and prepared in order to minimise the risk of surface contamination.

Measurement of outcome

The outcome of interest was HTN.

Hypertension

Hypertension was defined, for this study, as a systolic blood pressure of $\geq$ 140 mmHg or a diastolic blood pressure of $\geq$ 90 mmHg (WHO 1996).[23]

Blood pressure measurements were taken at rest in accordance with the protocol recommended by the Joint National Committee, 2003.[24] Blood pressure was measured three times, with the lowest value taken as the proper value for this study. Subjects found to have elevated blood pressure, had two further readings a few days later to validate the finding of hypertension.

Measurement of confounders

Demographic data were collected from each participant and information gathered on socioeconomic variables, addiction and BMI (Body mass Index). As most of the people were poor, with a paucity of education, they could not provide definite family histories of HTN, IHD or diabetes mellitus. However, as expected from our extensive

experience of working in this area, random spot testing of blood sugar levels was indicative of a low background prevalence of diabetes mellitus.

Statistical analysis

Data were first examined for difference in baseline characteristics such as age, indicators of socioeconomic condition and BMI. Data regarding arsenic exposure through drinking water, as well as biological measurements were compared across the two groups to cross-validate the exposure classification that had been made on the basis of area of residence. Statistical significance between groups was determined with significance level set at $P < 0.05$.

Subsequently, we carried out multivariate logistic regression (unconditional) analysis to look for difference in odds of HTN between Group- 1 and Group-2 participants. The regression model included age, sex, cumulative arsenic exposure, arsenic level in hair and BMI as potential confounders. Further, using data from Group-1 only, a multiple regression model was fitted to HTN to examine possible associations with: cumulative arsenic intake as exposure; hair arsenic level as a potential biomarker; presence of skin lesions; and age, sex, and BMI as potential confounders.

All other covariates like arsenic level in urine as biomarker and potential confounders such as occupation, housing, addictions like smoking and tobacco chewing and alcohol use were screened to determine whether or not they were significant risk factors or confounders. These were initially included in the regression but later dropped as they did not appear to show an association or confound the associations of interest. All statistical analyses were carried out using software Minitab, version 14.

Results and discussion

Baseline characteristics of the two study groups are given in Table 1. There was no significant difference between the two groups in relation to age, sex, smoking, tobacco chewing or BMI; a greater percentage of participants in the unexposed group used alcohol but absolute numbers were very small.

High exposure of arsenic through drinking water and high level of arsenic in urine and hair were observed in the people from area of groundwater contamination (Group 1), while the corresponding values in participants belonging to The non-contaminated area (Group 2) were normal. Distribution of participants among the two study groups in regard to values of systolic and diastolic blood pressure in different ranges is given in Table 2. Significant difference in systolic blood pressure in the range of 160–179 mmHg and diastolic blood pressure in the range of 90 to 99 were observed in arsenic-exposed people in comparison to unexposed people.

Age-stratified comparison of the two groups showed that there was no statistically significant difference in the prevalence of hypertension amongst the under 60s. However, amongst those over 60, there was a statistically significant

Table 1. Baseline characteristics and exposure data among participants in arsenic contaminated (Group 1) and uncontaminated (Group 2) region in West Bengal, India.

Baseline characteristics	*Exposed group 1 (n = 208) (%)*	*Unexposed group 2 (n = 100) (%)*	P-*value*
Age Classification:			
15–29	35 (16.83)	20 (20.00)	0.506
30–44	92 (44.23)	45 (45.00)	0.899
45–59	72 (34.62)	30 (30.00)	0.414
60–74	9 (4.33)	5 (5.00)	0.795
Sex :			
Male	126 (60.58)	60 (60.00)	0.923
Female	82 (39.42)	40 (40.00)	0.923
Addiction			
Smoking	58 (27.88)	32 (32.00)	0.463
Alcohol	0 (0.00)	4 (4.00)	0.011
Tobacco chewing	21 (10.10)	9 (9.00)	0.757
BMI Classification			
Under Weight (<18.50)	65 (31.25)	24 (24.00)	0.175
Normal (18.50 – 24.99)	122 (58.65)	61 (61.00)	0.694
Pre-Obese (25.00–29.99)	18 (8.65)	14 (14.00)	0.179
Obese(≥30)	3 (1.44)	1 (1.00)	1.000
Exposure data	Mean (Range)	Mean (Range)	
Current level of As in drinking water(μg/L)	49.66 (BDL – 326)	BDL	–
Cumulative Dose of As from water in mg/L- years	4.13 (BDL – 24.98)	BDL	
As in Urine (μg/L)	n = 204119.40 (12 – 526)	n = 99 16.71 (BDL – 37)	
As in Hair (mg/kg)	N = 206 1.18 (0.18 – 7.51)	0.18 (0.06 – 0.47)	

Table 2. Distribution of blood pressure in two study groups.

	Exposed group 1 (N = 208)		*Unexposed group 2 (N = 100)*		
Systolic B.P. Hg mm	*No.*	*%*	*No.*	*%*	P-*value*
(<130)	133	*63.94*	68	68	0.4793
(130–139)	30	*14.42*	13	13	0.7398
(140–159)	25	*12.02*	17	17	0.2310
(160–179)	17	*8.17*	1	1	0.0118
(≥180)	3	*1.44*	1	1	0.7691
Systolic Hypertension(≥140)	45	*21.63*	19	19	0.5983
Diastolic B.P. Hg mm					
(<85)	154	*74.04*	82	82.00	0.1205
(85–89)	9	*4.33*	6	6.00	0.5156
(90–99)	34	*16.35*	8	8.00	0.0466
100–109)	6	*2.88*	2	2.00	0.6426
≥110)	5	*2.40*	2	2.00	0.8253
Diastolic Hypertension(> = 90)	45	*21.63*	12	12.00	0.0421

association between prevalence of hypertension in Group-1 participants compared to Group-2 participants (Table 3). Stratifying by gender, there was statistically significant associations between arsenic exposure and HTN amongst males ($P < 0.001$) (Table 4).

Multivariate logistic regressions analysis comparing participants from the two groups showed increased odds ratios (OR) of HTN (Adjusted Odds Ratio, OR, 2.87 [95 % Confidence Interval, CI = 1.26–4.83]) in Group-1 compared to Group-2 (Table 5). Significant dose response relationship was observed with cumulative arsenic exposure through drinking water (unadjusted OR, 2.02[95 % CI = 1.02–3.99]) and arsenic level in hair (Unadjusted OR, 5.03[95 % CI = 1.96–12.93]) and HTN. Further, significant increasing risk of HTN was observed with increasing age, BMI. However, we did not find significant dose response relation with arsenic level in urine and hypertension.

Table 6 presented data of logistic regression analysis showing that there was significant association of HTN with arsenic level in hair (Regression Coefficient, 0.387275 [95 % CI = 1.08–2.01], $P < 0.01$). All the variables were tested and were found to be distributed as normal distribution.

The present study shows evidence of increased association of HTN (Adjusted Odds Ratio, OR, 2.87 [95 % Confidence Interval, CI = 1.26–4.83]) in individuals resident in an area of high groundwater contamination with arsenic (Nadia) compared to those from a non-contaminated area (Hoogly) in West Bengal. A significant dose response relationship was observed with cumulative arsenic exposure from drinking water and arsenic level in hair in relation to HTN in arsenic exposed subjects. Further logistic regression analysis showed that there was significant association of HTN with increased age, male sex, and higher BMI and arsenic level in hair. Occurrence of HTN was reported in 6.2 % of patients affected with arsenical skin lesions in 144 cases compared to none without skin lesion in 36 subjects in arsenic exposed people in Antafagesta, Chile.[14]

Increased prevalence of HTN among residents in the endemic area of black foot disease (BFD) and a dose-response relationship between ingested inorganic arsenic and prevalence of HTN were reported in epidemiological study in Taiwan.[13] A cross-sectional study of blood pressure in a population from Bangladesh with similar characteristics as ours demonstrated an association of average and cumulative arsenic exposure in drinking water with risk of HTN.[15]

Table 3. Age-stratified prevalence of hypertension (HTN) among participants in arsenic contaminated (Group 1) and uncontaminated (Group 2) region.

	HTN				
	Group-1		*Group-2*		
Age	*Total*	*Positive*	*Total*	*Positive*	P-*value*
15–29	35	7	20	2	>0.05
30–44	92	15	45	6	>0.05
45–59	72	30	30	9	>0.05
60–74	9	9	5	2	<0.01

Table 4. Prevalence of hypertension (HTN)) among participants of both sexes in arsenic contaminated (Group 1) and uncontaminated (Group 2) region.

	HTN				
	As exposed (Gr. 1)		*As unexposed (Gr. 2)*		
Sex	*Total*	*Positive*	*Total*	*Positive*	P-*value*
Male	126	30	60	8	<0.001
Female	82	31	40	12	>0.05

Table 5. Results of multivariate logistic regression analysis of HTN and IHD in participants living in arsenic contaminated and uncontaminated region (n = 308) with adjustment for age, sex, cumulative arsenic exposure, arsenic level in hair and BMI in West Bengal.

		HTN		
	Total	*HTN +*	*Unadj.odd ratio (95 % CI)*	*Adjusted odd ratio (95 % CI)*
Participants :				
Unxposed Group 2)	100	20	1	1
Exposed (Group 1)	208	61	1.66 (1.02–2.97)	2.87 (1.26–4.83)
Age:				
15–29	55	9	1.0	1.0
30–44	137	22	1.01 (0.41–2.28)	1.05 (0.42–2.63)
45–60	107	39	3.16 (1.39–7.17)	3.69 (1.49–9.18)
>60	9	11	18.74 (4.34–80.93)	29.10 (9.05–72.5)
Sex:				
Male	186	38	1.0	1.0
Female	122	43	2.12 (1.27–3.55)	2.69 (1.48–4.90)
Cumulative Dose of As from water in mg/L- years :				
0	100	20	1.0	1.0
0–4.5	136	37	1.49 (0.82–2.78)	1.65 (1.02–6.14)
>4.5	72	24	2.02 (1.02–3.99)	2.07 (0.64–6.57)
Hair in mg/Kg :				
0–0.18	59	12	1.0	1.0
0.19–2.0	217	51	1.21 (0.59–2.44)	1.37 (0.65–3.81)
>2.0	32	18	5.03 (1.96–12.93)	2.39 (0.57–10.00)
BMI :				
< 18.5	89	18	1.0	1.0
18.5–24.9	182	41	1.15 (0.61–2.14)	1.36 (0.67–2.74)
25–29.9	33	19	4.73 (2.01–11.17)	7.14 (2.52–20.53)
>30	4	3	7.54 (1.16–69.65)	9.29 (1.24–91.53)

All the investigators from Taiwan reported recruitment of their participants from areas of peripheral vascular disease (BFD) due to arsenic contaminated artesian well water. However, humic substances isolated from artesian well water in the BFD endemic areas of Taiwan have been found to be associated with thrombogenesis in experimental models.[7, 25, 26]

The contributory role of these substances in causing the observed cases of hypertension in Taiwan was not known. The evidence around the link between HTN and arsenic exposure were reported to be inconclusive. A systematic review of the epidemiological evidence on arsenic exposure and cardiovascular disease showed that methodological limitations limited interpretation of the moderate to strong association between high arsenic exposure and cardiovascular outcome in Taiwan. In other population and in occupational setting, the evidence was inconclusive.[20]

More reports are available on the link between HTN and chronic arsenic exposure outside Taiwan. In a study from Bangladesh, though the investigators found arsenic exposure was positively associated with systolic hypertension and high pulse pressure, no apparent association was observed between time-weighted well arsenic concentration (TWA) and general or diastolic hypertension.[27] In a cross-sectional study conducted on 8790 women who had recently been pregnant in an area of Inner Mongolia, China showed

Table 6. Results of Multivariate Logistic Regression analysis evaluating association of HTN with cumulative arsenic intake, hair arsenic level and presence of skin lesions; and age, sex, and BMI as potential confounders in participants living in arsenic contaminated region.

Predictor	*Coefficient*	*P*	*Odds ratio*	*95 % Lower*	*CI upper*
Constant	−9.95163	0.000			
Age	0.106427	0.000	1.11	1.07	1.16
Sex	0.911548	0.016	2.49	1.19	5.21
Skin Lesion	−0.0943702	0.798	0.91	0.44	1.87
Cumulative As intake	−0.0502950	0.299	0.95	0.86	1.05
Hair	0.387275	0.015	1.47	1.08	2.01
BMI	0.188520	0.001	1.21	1.08	1.35

that increased systolic and diastolic blood pressure levels were associated with increasing drinking water arsenic, the lowest exposure level being 21 to 50 μg/L.[28] However, at the low to moderate levels, typical of the U.S. population, total arsenic, total arsenic minus arsenobetaine, and DMA concentrations in urine were not associated with the prevalence of hypertension or with systolic or diastolic blood pressure levels.[29]

Our study supports an association between arsenic exposure and HTN in individuals resident in arsenic endemic area compared to those from a non-endemic area. However, we did not notice dose-response relationships with arsenic level in urine and HTN in Group-1 participants.

Many participants in the arsenic endemic region are currently drinking water with arsenic level within safe limit. Urinary arsenic level is a marker of more recent exposure whereas hair arsenic level is indicative of chronic exposure. It is therefore plausible that due to the long lead times between exposure to risk factors and development of cardiovascular outcomes, the correlation seen with hair levels is not replicated with urine levels.

The strength of this research was that both assessment of exposure and biomarker and outcome were linked at the level of the individual within two study populations drawn from regions with and without groundwater arsenic contamination. Arsenic levels in urine and hair were measured in all participants across both groups and correlated with occurrence of HTN.

A major limitation of this research is the lack of ascertainment of key confounding factors like family history of cardiovascular disease and diabetes mellitus; this information was not consistently available from the study participants, who were poorly educated and lived in poverty. Neither were we able to test blood glucose levels or lipid profiles consistently across the entire study population for logistical reasons, although random spot testing of blood sugars suggested a low background prevalence of diabetes mellitus.

Other limitations are proper assessment of cumulative arsenic exposure through drinking water. Retrospective estimation of lifetime exposure through drinking water is subject to recall bias. Concerns around using hair as well as nails as biomarkers relate to the possibility of surface contamination by adsorbed metals. In this study, every precaution was taken to ensure that all surface contamination was removed. In the event of any residual artefact in spite of the preparatory steps taken, we would anticipate that any potential bias would be non-differential across the exposed group. Moreover, there are no alternative biomarkers available by which to estimate chronic exposure of arsenic and both hair and nail are widely used.

Conclusion

This study shows that HTN occur in a significant number of arsenic exposed participants compared to unexposed controls. A strong dose-response effect was observed with increasing levels of arsenic in hair with HTN. Many of the limitations in the study are due to the logistical difficulties in conducting research in a remote and rural area. Nonetheless, the findings support an association between adverse cardiovascular outcomes like HTN and arsenic exposure. Further work is needed in this area.

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