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Full Length Research Paper

Ischemic heart disease in chronic arsenic exposure: A case control study in West Bengal

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Reports of cardiovascular complications due to chronic arsenic exposure are scanty from the Indo-Bangladesh subcontinent. This study from West Bengal, India assesses the likelihood of ischemic heart disease (IHD) in individuals resident in an area of high groundwater contamination with arsenic (Nadia district) compared to those from a non-contaminated area (Hoogly district). 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 and electrocardiography were done 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 showed evidence of increased association of IHD in individuals resident in arsenic endemic region compared to those from a non-endemic region with increased odds ratio for IHD (Adjusted Odds Ratio, OR 2.14 (95%CI=(1.03-4.15)) in Group- 1 participants compared to Group- 2. Within Group 1, there was no difference in prevalence of cardiovascular outcomes between those with and without skin lesion. There was a dose-effect relationship seen with increasing arsenic level in hair and IHD (Unadjusted OR. 4.31 (95%CI=(1.01-18.58)) in participants living in arsenic endemic region. The findings reported here support an association between arsenic exposure and IHD. More work is needed to characterize the link further.

Keywords: Arsenic and ischemic heart disease. Arsenic in hair, Arsenic in heart disease, 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 are the basin of the Ganga-Brahmaputra-Meghna Rivers (Chakraborti, D 2004) and the Mekong Delta (GuhaMazumder et al., 2009). Though 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 (Garai et al., 1984).

Besides pigmentation and keratosis, arsenicosis produces systemic manifestations including chronic

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respiratory disease, peripheral neuropathy, liver fibrosis, edema of legs, anemia and cancers. (GuhaMazumder et al. (1988, 1998, 2001), NRC, 1999; WHO, 2005). 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) (Tseng et al. (1961, 1968), Engel, et al., 1994a, Engel, 1994b).Increased mortality rate from ischemic heart disease (IHD) has been reported among residents in BFD endemic regions of Taiwan. (Chen, et al. (1988, 1994, 1996). Long-term arsenic exposure was found to be associated with IHD, diagnosed by resting electrocardiograms in a community based study in the BFD-endemic villages of Taiwan. History of arsenic exposure was estimated through information obtained from the arsenic content in artesian well water of the villages (Tseng, et al 2003). 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 (Navas-Acien et al., 2005).

In this community based study association of IHD was ascertained on the basis of interpretation of electrocardiograms 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 cardiovascular disease.

MATERIAL AND METHODS

This study determined the cardiovascular endpoint, IHD, 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 ground water was not contaminated with arsenic (arsenic level in ground water below detection limit, < 3 µg/L).

Subject Selection

208 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 (GuhaMazumder et al., 2010) 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,) age and sex matched with the participants belonging to Group-1 were recruited from one village in the Hoogly district, West Bengal without having arsenic contamination (arsenic level in ground water <3µg/L).

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 (WHO, 2005) and Electrocardiogram was done in each of the participant.

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_i x 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 until further analysis (WHO, 2005).

Arsenic levels in urine, hair and water were measured

Box 1. ECG criteria used in ascertainment of Ischemic heart disease (IHD)

ECG criteria used in ascertainment of cases of coronary heart disease (IHD)	
Myocardial ischaemia	Combination of (a) ST depression of > or = 1mm (0.10mV) at the J point AND (b) A horizontal or downward slope towards the end of the ST segment at its junction with the T wave In at least one of the 12 standard ECG leads.
Myocardial infarction (established)	Presence of pathological Q wave in the absence of (a) ventricularhypertophy, (b) intraventricular conduction abnormality (c) ventricular pre-excitation

using an atomic absorption spectrophotometer with a flow-injection hydride generation system as described by (Das et al.,1995). The limit of detection determined at the 90% confidence level was 3µg/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 ECG changes consistent with IHD.

Electrocardiography

Twelve lead standard electrocardiograms (ECG) were taken in the field with a portable battery operated multi-channel computerized ECG recorder (Vega, LandT Ltd., India). A total of 205 ECGs were taken from exposed subjects in Group 1, and 100 ECGs from unexposed subjects in Group 2.

Tracings were first examined for quality. Tracings were eliminated if they were of poor quality, that is if there were baseline artefacts, or marked tachycardia with P on T; or if there were confounding ECG abnormalities such as non-sinus rhythm or frequent ectopic. All ECGs assessed to be of reasonable quality were evaluated by a cardiologist (GM) who was blind to whether the ECG was from a participant in Group 1 or 2.

The ECG criteria used in ascertainment of IHD disease status are described in Box1. Graphic interpretation followed the Minnesota code of classification for ECG findings (Blackburn et al., 1960).

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. These data are reported as Means $\pm$ S.D. 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 IHD 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 IHD 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 co-variates 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.

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) N (%)	Unexposed Group 2 (N = 100) N (%)	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			
Current level of As in drinking water(µg/L) Mean±SD	49.66±60.33	BDL	-
Cumulative Dose of As from water in mg/L- years	4.13 ± 4.14		
As in Urine (µg/L) Mean±SD	117.67 ± 94.71	17.17 ± 11.39	p<0.001
As in Hair (mg/kg) Mean±SD	1.18 ± 1.09	0.18 ± 0.09	p<0.001

Table 2. Prevalence of ischemic heart disease (IHD), stratified by age, among participants in arsenic contaminated (Group 1) and uncontaminated (Group 2) region

	IHD				
	Group- 1		Group- 2		
Age	Total	Positive	Total	Positive	p-value
15 – 29	35	1	20	3	>0.05
30 – 44	92	5	45	2	>0.05
45 – 59	72	10	30	2	>0.05
60 – 74	9	3	5	0	<0.05

RESULTS

Baseline characteristics of the two study groups are given in the 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 non–contaminated area (Group 2) were within normal limit. Age stratified comparison of the two groups showed that there was no statistically significant difference in the prevalence of IHD amongst the under 60s. However, amongst those over 60, there was a statistically significant association between prevalence of IHD in Group-1 participants compared to Group-2 participants (Table 2). Stratifying by gender, there was no statistically significant associations between arsenic exposure and IHD (Table 3).

Multivariate logistic regressions analysis comparing participants from the two groups showed increased odds

Table 3. Prevalence of ischemic heart disease (IHD) among both sexes in arsenic contaminated (Group 1) and uncontaminated (Group 2) region

Sex	IHD				p-value
	As Exposed (Gr. 1)		As Unexposed (Gr. 2)		
	Total	Positive	Total	Positive	
Male	126	12	60	3	>0.05
Female	82	7	40	3	>0.05

Table 4. Results of multivariate logistic regression analysis of IHD in participants (n= 308) living in arsenic contaminated and uncontaminated region in West Bengal, adjusted for age, sex, cumulative arsenic exposure, arsenic level in hair and BMI.

	Total	IHD		
		.IHD+	Unadj. Odd Ratio (95% CI)	Adjusted Odd Ratio (95% CI)
Participants:				
Unxposed	100	6	1	1
Exposed	208	19	1.57 (0.61-4.08)	2.14 (1.03-4.15)
Age				
15-29	55	4	1.0	1.0
30-44	137	7	0.69 (0.19-2.45)	0.89 (0.25-3.24)
45-60	107	12	1.61 (0.49-5.25)	1.76 (0.50-6.23)
>60	9	2	3.64 (0.56-23.69)	6.43 (1.06-39.07)
Sex				
Male	186	15	1.0	1.0
Female	122	10	1.02 (0.44-2.36)	1.06 (0.45-2.52)
Cumulative Dose of As from water in mg/L- years:				
0	100	6	1.0	1.0
0 – 4.5	136	15	1.94 (0.91-5.19)	1.42 (0.46-4.38)
>4.5	72	4	0.93 (0.27-3.39)	0.51 (0.12-2.04)
Hair mg/Kg:				
0-0.18	59	3	1.0	1.0
0.19-2.0	217	16	1.49 (0.42-5.28)	1.31 (0.26-6.67)
>2.0	32	6	4.31 (1.01-18.58)	4.10 (0.57-29.35)
BMI:				
< 18.5	89	7	1.0	1.0
18.5 – 24.9	182	1 4	0.97 (0.38-2.51)	1.32 (0.47-3.68)
25 – 29.9	33	4	14.06 (5.01-39.45)	2.12 (0.52-8.58)
>30	4	0	-	-

ratios (OR) of IHD (Adjusted OR, 2.14 [95% CI=1.03-4.15]) in Group-1 compared to Group- 2 (Table 4). Significant dose response relationship was observed with arsenic level in hair (Unadjusted OR, 4.31[95% CI=1.01-

Table 5. Results of Multivariate Logistic Regression analysis evaluating association of IHD 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	-8.23065	0.001			
Age	0.122795	0.000	1.13	1.06	1.21
Sex	-0.232885	0.708	0.79	0.23	2.68
Skin Lesion	-0.454842	0.446	0.63	0.20	2.04
Cumulative As intake	-0.141956	0.088	0.87	0.74	1.02
Hair	0.461581	0.026	1.59	1.06	2.38
BMI	0.0192163	0.812	1.02	0.87	1.19

18.58]) and IHD. Further, significant increasing risk of IHD was observed with increasing age and BMI.

Table 5 presented data of logistic regression analysis showing that there was significant association of IHD with arsenic level in hair (Regression Coefficient, 0.461581 [95% CI=1.06-2.38], $p<0.05$). All the variables were tested and were found to be distributed as normal distribution.

No significant difference was observed in regard to prevalence of IHD among exposed cases with skin lesion compared to exposed subjects without skin lesion. There was also no difference in age distribution, sex, arsenic exposure through drinking water and arsenic level in urine and hair among arsenic exposed participants with and without skin lesion. This was broadly in keeping with the exposure assessment made on the basis of residence.

DISCUSSIONS

The present study showed evidence of increased association of IHD 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 arsenic level in hair in relation to IHD in arsenic exposed subjects. Further logistic regression analysis showed that there was significant association of IHD with age and arsenic level in hair.

Some reports are available regarding association of chronic arsenic exposure and IHD. A study undertaken between 1973 and 1986, in the black foot disease (BFD) endemic regions of Taiwan demonstrated higher mortality due to IHD associated with increasing arsenic level in drinking water. No significant association was found with cigarette smoking and BMI (Chen, et al., 1996).However, this study did not link exposure and outcome assessment at the individual level. In another study from Taiwan, significant association of IHD by electrocardiography was reported following long-term exposure of arsenic in a community based study in the (BFD)-endemic villages(Tseng et al., 2003).

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 (NRC., 1999, Lu et al., 1990, Yang et al., 1996) The contributory role of these substances in causing the observed cases of IHD in Taiwan was not known. The evidence around the link between IHD 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 ((Navas-Acien et al., 2005). More reports are available on the link between IHD and chronic arsenic exposure outside Taiwan. In a retrospective study increased risk of mortality due to acute myocardial infarction (AMI) was found in an arsenic-exposed region of Chile during the high-exposure period from 1958 to 1970 (Yuan et al.,2007). Further, an ecological study carried out in Spain showed increased cardiovascular mortality at the municipal level with mild to moderate elevated arsenic concentrations in drinking water. Standardized mortality ratios (SMRs) for IHD (113,000 deaths), were analysed covering 24.8 million people. Mean municipal drinking water arsenic concentrations ranged from <1 to 118 µg/L. Compared to the overall Spanish population, sex- and age-adjusted mortality rates for IHD (SMR 1.18) were increased in municipalities with arsenic concentrations in drinking water > 10 µg/L (Medrano et al., 2010). A study from Bangladesh showed increased cardiovascular mortality due to arsenic exposure. There was a dose-response relationship between exposure to arsenic in well water assessed at baseline and mortality from IHD (Chen et al 2011).

Our study supports an association between arsenic

exposure and IHD 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 IHD in Group-1 participants. Further, no such relationship was observed with IHD and cumulative arsenic exposure through drinking water.

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 paper 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 ground water arsenic contamination. Arsenic levels in urine and hair were measured in all participants across both groups and correlated with occurrence of IHD. The presence of ischemic heart disease was assessed objectively by taking electrocardiograms from each participant and this was one of the few studies in which non-fatal cardiovascular endpoints had been studied.

Major limitation of this paper 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. Further potential inaccuracies in the history and non-availability of water from some of the tube wells used in the past because of closure may be reflected in the lack of dose-response seen with cumulative arsenic intake and IHD in our study. 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 IHD 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 IHD. 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 and arsenic exposure. Further work is needed in this area.

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