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Systemic manifestations in chronic arsenic toxicity in absence of skin lesions in West Bengal

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***Background & objectives*: Pigmentation and keratosis are the prerequisites to diagnose arsenicosis. However, many systemic manifestations occur in association with pigmentation and keratosis in people exposed to chronic drinking of arsenic contaminated water. The present study aim to find out whether systemic manifestations occur in significant number of cases in arsenic exposed people in the absence of skin lesions in an affected district in West Bengal, India.**

***Methods*: A cross-sectional study was carried out in South 24 Parganas, an arsenic affected district of West Bengal, India. Both dermatological and systemic manifestations were recorded and water samples collected for arsenic analysis from 7683 participants. A correlation of systemic manifestations in relation to arsenic exposure was carried out in subjects having no arsenical skin lesion. Prevalence odds ratio (POR) was calculated for each outcome comparing those with high arsenic exposure with those with lowest exposure.**

***Results*: The frequency of occurrence of various clinical manifestations like weakness, anaemia, diarrhoea, hepatomegaly and lung disease was found to be significantly higher among participants drinking water having arsenic concentration ≥ 50 µg/l in comparison to those taking water with arsenic content below this level. Further, there was increased occurrence of these manifestations with increasing concentration of arsenic level in drinking water, and this followed a dose-response relationship.**

***Interpretation & conclusion*: It appears that it is worthwhile to include people with systemic manifestations in absence of skin lesions with evidence of arsenic exposure as suspected cases of arsenicosis for case detection and in surveillance programme.**

Key words Absence of skin lesions - chronic arsenicosis - dose response - systemic manifestations

Many aquifers in various regions of the world are contaminated with arsenic (As) at concentration above 50 µg/l. Of these, the most noteworthy occurrences are in West Bengal (India), Bangladesh, Taiwan, Northern China, Hungary, Mexico, many parts of the USA, Chile and Argentina[1]. Though chronic arsenic toxicity due to drinking of arsenic contaminated water has been reported from many countries, reports of large number of affected people in West Bengal, India and Bangladesh are unprecedented[2]. The source of the contamination is geological; arsenic in ground water has been found above 50 µg/l (the current drinking water standard in the country) in eight of the 16 districts of West Bengal[3]. More than 40 million people live in

this arsenic affected region of the State. It is suspected that about 5 million people drink arsenic contaminated water in West Bengal[3].

Prolonged ingestion of arsenic-contaminated water is reported to produce not only pigmentation and keratosis, but also many systemic features like weakness, anaemia, chronic lung disease, conjunctival congestion, hepatomegaly and non cirrhotic portal fibrosis, polyneuropathy, chronic diarrhoea, dyspepsia, solid oedema of limbs, gangrene of toes, and skin cancer and other malignant neoplasms[4-6]. Skin characteristics change and pigmentation and keratosis have long been known to be hallmark signs of chronic arsenic exposure[7]. These lesions are the most common health effect found in populations exposed to arsenic-contaminated drinking water in Chile, Argentina, Mexico and various countries of Asia[1]. The pigmentation is marked by raindrop-shaped discolored spots, diffuse dark brown spots or diffuse darkening of the skin on the limbs and trunk. Simple keratosis usually appears as bilateral thickening of the palms and soles, while in nodular keratosis, small protrusions appear in the hands, feet, or the legs[7,8].

According to WHO algorithm, presence of skin lesion *i.e.,* either pigmentation or keratosis or both is essential for diagnosing a patient as a case of arsenicosis[7]. However, many systemic manifestations also occur in people exposed to arsenic toxicity in addition to skin lesions. The present study was conducted to find out whether systemic manifestations occur in significant number of cases in arsenic exposed population even in the absence of skin manifestation in a district in West Bengal, India

Material & Methods

Study area and population: Two particular areas within the district of South 24 Parganas, West Bengal, India were targeted for the study. The first area was selected because high levels of arsenic were reported to occur in some shallow tube wells, in some of the villages, but not in all, as determined in a prior study (Report, Government of West Bengal, 1994). The second area included the remaining parts of the district where people used shallow tube well water for drinking purposes. The two areas combined had a total population of 150457. It was decided to include 5 per cent of the population in the study as no earlier report on prevalence of arsenicosis was available from this area.

The high exposure region included 25 villages. As the contamination of tube wells was not uniformly distributed in the villages, convenience sampling was used which involved remote rural areas. The study team went to the centre of each village and selected the most convenient hamlet (group of houses) to commence sampling. Each member of the household present at the time of the interview was invited to participate. An interview was taken based on a pre-designed and pre-tested questionnaire and a brief medical examination was conducted. Sampling continued house-to-house in a village until 50 to 150 participants were recruited depending on the population of the village.

The low exposure region included 32 villages within 16 administrative blocks. Sampling in this region was restricted to villages with more than 100 houses. One or more villages were selected at random from each of the 16 blocks depending on the population size. Only one village was selected for sampling from a small block, but two or three villages were selected if the block was large. The number of villages allocated in each block was made by proportional allocation depending upon the number of villages in the block. The sample village in each block was selected randomly with probability proportional to the size method. The size of the village referred to was based on the total population of the village. The households in a sample village were selected by systematic sampling with a random start procedure.

Interview and medical examination: The field survey was designed to minimize subjectivity in examining the participants. Field workers inevitably knew if a village they were working in was located in the high exposure area or the low exposure area, but they did not know the tube well arsenic concentrations at the time of the survey. Each participant was interviewed by a trained field worker. History regarding drinking water consumption, tube well water source was taken and recorded. Medical history of the participants was taken by a physician to find out presence or absence of any symptom like weakness, cough, respiratory distress, chronic diarrhoea, *etc*., and the general medical examination was performed to elicit presence of pallor, hepatomegaly, chest signs, *etc*. An examination of skin was done to determine skin lesions characteristic of chronic arsenic toxicity. Other skin diseases simulating arsenicosis were excluded to diagnose arsenical skin disease. Height and weight of the participants were also taken.

Skin lesions characteristic of arsenicosis are quite distinctive. Arsenical keratoses was diagnosed by noting diffuse bilateral thickening of palms and/or soles with or without nodules of various shapes and sizes. Hyperpigmentation was identified if there was mottled dark brown pigmentation (rain drop pigmentation) bilaterally distributed on the trunk and limbs. Sometimes hyperpigmentation was present alongside spots of depigmentation, (leucomelanosis), but these characteristics were not regarded as essential for the diagnosis. Anaemia was diagnosed by observing pallor in the palpabral conjunctiva. Chronic lung disease was diagnosed if history of episodes of cough for a period with or without history of breathing difficulty or chest signs on auscultation present. Hepatomegaly was considered if the liver was palpable for more than 2 cm below the costal arch in the mid clavicular line. All patients were examined in the field by one of two physicians who have had about 10 years experience in diagnosing arsenic-caused skin lesions in West Bengal, including examining patients regularly in the Arsenic Clinic in the hospital linked with a Post Graduate Medical Institute in Kolkata.

Water sampling and arsenic measurement: Water samples were collected from private and public tube wells used for drinking and cooking purposes by each recruited household. Arsenic levels were measured by flow-injection hydride generation atomic absorption spectrophotometer (Parkin & Elmer).

Of the 7683 participants (4093 females and 3590 males) 361 were found to have arsenical skin lesions. Information on various systemic manifestations in arsenic exposed and unexposed people was available from 7276 of 7322 subjects without any skin lesion and constituted the study group.

Statistical analysis: The outcomes analysed included participant-reported and physician recorded systemic manifestations: weakness, anaemia, chronic lung disease, diarrhoea and hepatomegaly. To allow for direct comparisons in relation to age, the prevalence of each outcome was tabulated in relation to age distribution of study group of the same sex. Each outcome was examined according to arsenic levels in the tubewell drinking water source used by each participant. The tube wells were categorized according to arsenic concentrations as follows: <50, 59-199, 200-499, 500-799 and ≥ 800 μg/l.

Tests for trend in proportions using midpoints of exposure categories were based on the χ^2 distribution. Prevalence odds ratio (POR) were also calculated for each outcome comparing those with very high exposure to arsenic in drinking water (>500 μg/l) with those with lowest exposure (<50 μg/l).

Results

Prevalence of systemic manifestations was studied on 7276 people living in an arsenic endemic district of West Bengal who did not have evidence of arsenical skin lesion. Of these, 3825 people were found to be drinking water contaminated with arsenic ≥ 50 μg /l while 3451 people were taking safe water (arsenic level <50 μg /l).

Table I presents the age and sex distribution of all study participants by arsenic level in drinking water. The arsenic concentration in tube well water samples ranged from <3 to 3400 μg/l.

The overall prevalence of weakness increased strongly with higher arsenic concentration in both sexes (from 1.6 per 100 to 7.7 per 100 among women among the lowest and highest exposure category respectively, test of trend, P=0.027, and from 0.9 per 100 to 5 per 100 among men, P=0.027, Table II).

Overall prevalence of anaemia and lung disease also increased with increase of arsenic concentration in both sexes. For anaemia and lung disease, the prevalence in women increased from 3.6 and 4.7 per

Table I. Distribution of population according to age, sex and arsenic level in drinking water (μg/l)

Age group	Arsenic level in water (μg/l)					
(yr)	< 50	50-199	200-499	500-799	≥ 800	Total
Female:						
≤ 9	161	81	103	70	24	439
10 - 19	365	163	156	68	23	775
20 - 29	537	253	160	65	19	1034
30 - 39	333	180	122	60	13	708
40 - 49	196	87	57	25	9	374
50 - 59	162	68	37	26	6	299
≥ 60	150	80	60	18	9	317
Total	1904	912	695	332	103	3946
Male:						
≤ 9	189	125	95	82	22	513
10 - 19	331	169	127	65	29	721
20 - 29	295	162	94	47	14	612
30 - 39	271	135	95	43	10	554
40 - 49	184	83	65	26	11	369
50 - 59	111	64	35	17	7	234
≥ 60	166	84	55	15	7	327
Total	1547	822	566	295	100	3330

100 to 15.0 and 9.3 per 100 (exposure category <50 μg /l to 799 μg/l) though the prevalence was lower (5.8 and 3.8) in the highest exposure category (≥800 μg /l) respectively (*P*=0.65 and 0.87 respectively). For males the prevalence were 2.0 and 11.5 per 100 to 9 and 17 per 100 respectively (*P*=0.33 and 0.45 respectively). The prevalence of anaemia was found to be higher and that of lung disease lower in women compared to men, but these were not statistically significant (Tables III, IV).

Among females, the overall prevalence of diarrhoea and hepatomegaly were 0.7 and 2.6 per 100 in the lowest exposure category and increased with increase of arsenic exposure, the prevalence in the highest exposure category being 3.8 and 12.6 per 100 respectively (*P*=0.04 and 0.004 respectively). In males the values were higher, prevalence being 0.5 and 3.1 respectively in the lowest exposure category to 4 and 18 per 100 respectively in the highest exposure category (*P*=0.01 and 0.004 respectively) (Tables V, VI).

Table VII gives prevalence odds ratio (POR) comparing the highest exposure category (≥500 μg/l) with the lowest exposure category (<50 μg/l). All POR were elevated except for lung disease in males. Increased POR was seen in both females and males for weakness (5.48 and 5.24 respectively), aneamia (3.85 and 2.41 respectively) diarrhoea (5.49 and 4.97 respectively) and hepatomegaly (4.34 and 5.13 respectively). The POR for chronic lung disease for women was found to be 1.76.

Discussion

A cross-sectional study was carried out in South 24 Parganas, one of the severe arsenic affected districts of West Bengal, India, to ascertain the prevalence of systemic manifestations in absence of dermatological features of chronic arsenic toxicity. This study showed that systemic features like weakness, anaemia, chronic lung disease, chronic diarrhoea and hepatomegaly might occur in chronic arsenic exposed people even in absence of dermatological manifestations. This was further substantiated by observing high POR for each of these effects for both women and men (except for lung disease in males) comparing those exposed to arsenic ≥500 μg/l to participants exposed to <50 μg/l.

Systemic manifestations in association with dermatological lesions have been described in many reports in cases of chronic arsenic exposure. Generalized weakness and fatigue have been reported in people chronically exposed to arsenic contaminated drinking water[4,9-13]. Though anaemia was described in some reports of chronic arsenic exposure in humans[4,7,14,15], others did not find such abnormality[16-18]. The role of chronic ingestion of arsenic in the genesis of chronic lung disease has been suggested in several case studies and epidemiological investigations[13,19-26]. Further, in several studies lung function tests carried out on people exposed to arsenic showed evidences of restrictive and/or obstructive lung disease[21,27,28]. In a

Table II. Prevalence of weakness per 100 among people without any arsenical skin lesion by age group and arsenic level in water

Age group (yr)	Arsenic level in water (μg/l)					
	< 50	50-199	200-499	500-799	≥ 800	Total
Female:						
≤ 9	0 (0)	1.2 (1)	0.9 (1)	0 (0)	4.1 (1)	0.6 (3)
10 - 19	0.8 (3)	1.2 (2)	0.6 (1)	2.9 (2)	4.3 (1)	1.1 (9)
20 - 29	1.1 (6)	2.7 (7)	5 (8)	18.4 (12)	5.2 (1)	3.2 (34)
30 - 39	1.8 (6)	3.8 (7)	6.5 (8)	5 (3)	7.6 (1)	3.5 (25)
40 - 49	1.5 (3)	6.8 (6)	8.7 (5)	16 (4)	0 (0)	4.8 (18)
50 - 59	5.5 (9)	4.4 (3)	8.1 (3)	19.2 (5)	33.3 (2)	7.3 (22)
≥ 60	3.3 (5)	10 (8)	10 (6)	22.2 (4)	22.2 (2)	7.8 (25)
Total	1.6 (32)	3.7 (34)	4.6 (32)	9.0 (30)	7.7 (8)	3.4 (136)
Male:						
≤ 9	0.5 (1)	0.8 (1)	1.1 (1)	0 (0)	0 (0)	0.5 (3)
10 - 19	0.3 (1)	0.5 (1)	0 (0)	4.6 (3)	3.4 (1)	0.8 (6)
20 - 29	0.6 (2)	3.0 (5)	4.2 (4)	6.3 (3)	7.1 (1)	2.4 (15)
30 - 39	1.4 (4)	1.4 (2)	6.3 (6)	6.9 (3)	0 (0)	2.7 (15)
40 - 49	1.6 (3)	6.0 (5)	6.1 (4)	7.6 (2)	9.0 (1)	4.0 (15)
50 - 59	0.9 (1)	6.2 (4)	11.4 (4)	5.8 (1)	0 (0)	4.2 (10)
≥ 60	1.8 (3)	11.9 (10)	7.2 (4)	13.3 (2)	28.5 (2)	6.4 (21)
Total	0.9 (15)	3.4 (28)	4.0 (23)	4.7 (14)	5 (5)	2.5 (85)

Numerals in parentheses denote number of cases

case control study, a ten-fold higher rate of occurrence of bronchiectasis (detected by high resolution computerized tomography) was reported in cases with skin lesion compared to control subjects[29].

With chronic exposure to arsenic, overt gastrointestinal symptoms are often absent[7]. Gastroenteritis was reported in a study of 1447 cases of chronic arsenicosis caused by drinking arsenic contaminated water (50-1800 µg/l) in the Inner Mongolian Autonomous region of China[24]. Chronic diarrhoea has been reported to occur following chronic ingestion of arsenic contaminated water[4,19-21,24,30,31]. Several investigators have also reported cases of liver disease in the form of non cirrhotic portal

Table III. Prevalence of anaemia per 100 people without any arsenical skin lesion by age group and arsenic level in water

Age group (yr)	Arsenic level in water (µg/l)					
	< 50	50-199	200-499	500-799	≥ 800	Total
Female:						
≤ 9	4.9 (8)	8.6 (7)	6.7 (7)	2.8 (2)	4.1 (1)	5.6 (25)
10 - 19	1.6 (6)	13.4 (22)	10.8 (17)	11.7 (8)	4.3 (1)	6.9 (54)
20 - 29	3.3 (18)	9.4 (24)	11.8 (19)	12.3 (8)	0 (0)	6.6 (69)
30 - 39	3.6 (12)	10.5 (19)	17.2 (21)	23.3 (14)	7.6 (1)	9.4 (67)
40 - 49	5.1 (10)	9.1 (8)	22.8 (13)	28 (7)	22.2 (2)	10.6 (40)
50 - 59	4.9 (8)	10.2 (7)	18.9 (7)	19.2 (5)	0 (0)	9.0 (27)
≥ 60	5.3 (8)	15 (12)	20 (12)	33.3 (6)	11.1 (1)	12.3 (39)
Total	3.6 (70)	10.8 (99)	13.8 (96)	15.0 (50)	5.8 (6)	8.1 (321)
Male:						
≤ 9	3.1 (6)	15.2 (19)	5.2 (5)	4.8 (4)	9.0 (2)	7.0 (36)
10 - 19	2.1 (7)	5.3 (9)	8.6 (11)	3.0 (2)	10.3 (3)	4.4 (32)
20 - 29	1.6 (5)	6.7 (11)	4.2 (4)	4.2 (2)	14.2 (2)	3.9 (24)
30 - 39	1.8 (5)	4.4 (6)	9.4 (9)	2.3 (1)	0 (0)	3.7 (21)
40 - 49	2.1 (4)	9.6 (8)	13.8 (9)	3.8 (1)	0 (0)	5.9 (22)
50 - 59	0 (0)	4.6 (3)	5.7 (2)	5.8 (1)	0 (0)	2.5 (6)
≥ 60	3.0 (5)	2.3 (2)	14.5 (8)	0 (0)	28.5 (2)	5.1 (17)
Total	2.0 (32)	7.0 (58)	8.4 (48)	3.7 (11)	9 (9)	4.7 (158)

Numerals in parentheses denote number of cases

Table IV. Prevalence of lung disease per 100 people without any arsenical skin lesion by age group and arsenic level in water

Age group (yr)	Arsenic level in water (µg/l)					
	< 50	50-199	200-499	500-799	≥ 800	Total
Female:						
≤ 9	1.2 (2)	2.4 (2)	5.8 (6)	2.8 (2)	0 (0)	2.7 (12)
10 - 19	3.0 (11)	6.1 (10)	7.6 (12)	4.4 (3)	0 (0)	4.6 (36)
20 - 29	3.1 (17)	3.5 (9)	11.2 (18)	6.1 (4)	0 (0)	4.6 (48)
30 - 39	4.8 (16)	6.6 (12)	10.6 (13)	10 (6)	7.6 (1)	6.7 (48)
40 - 49	6.6 (13)	5.7 (5)	14.0 (8)	4 (1)	11.1 (1)	7.4 (28)
50 - 59	9.8 (16)	7.3 (5)	2.7 (1)	34.6 (9)	0 (0)	10.3 (31)
≥ 60	10 (15)	11.2 (9)	33.3 (20)	33.3 (6)	22.2 (2)	16.4 (52)
Total	4.7 (90)	5.7 (52)	11.2 (78)	9.3 (31)	3.8 (4)	6.4 (255)
Male:						
≤ 9	3.1 (6)	3.2 (4)	3.1 (3)	3.6 (3)	4.5 (1)	3.3 (17)
10 - 19	2.7 (9)	5.3 (9)	13.3 (17)	4.6 (3)	10.3 (3)	5.6 (41)
20 - 29	12.5 (37)	11.1 (18)	11.7 (11)	4.2 (2)	7.1 (1)	11.2 (69)
30 - 39	14.0 (38)	8.1 (11)	16.8 (16)	18.6 (8)	20 (2)	13.5 (75)
40 - 49	19.0 (35)	15.6 (13)	15.3 (10)	7.6 (2)	18.1 (2)	16.8 (62)
50 - 59	18.0 (20)	17.1 (11)	28.5 (10)	23.5 (4)	28.5 (2)	20.0 (47)
≥ 60	20.4 (34)	23.8 (20)	27.2 (15)	26.6 (4)	85.7 (6)	24.1 (79)
Total	11.5 (179)	10.4 (86)	14.4 (82)	8.8 (26)	17 (17)	11.7 (390)

Numerals in parentheses denote number of cases

fibrosis (NCPF) following treatment with trivalent inorganic arsenic has also been reported[32]. NCPF in liver following drinking of arsenic contaminated water was reported as early as 1978[33]. Since then hepatomegaly associated with prolonged intake of arsenic contaminated water has been reported by many authors[4,10,11,15,21,23,24,34,35].

Though there are many reports on various systemic manifestations due to chronic arsenic toxicity, very few reports are available on these features in absence of arsenical skin lesion[22]. In an earlier analysis of non-smokers of the same population, it was observed that the respiratory effects were largely confined to those who had arsenical skin disease, though weakness was

Table V. Prevalence of diarrhoea per 100 people without any arsenical skin lesion by age group and arsenic level in water

Age group (yr)	Arsenic level in water (µg/l)					
	< 50	50-199	200-499	500-799	≥ 800	Total
Female:						
≤ 9	1.2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0.4 (2)
10 - 19	0.2 (1)	0 (0)	0 (0)	5.8 (4)	0 (0)	0.6 (5)
20 - 29	0.5 (3)	1.5 (4)	1.8 (3)	3.0 (2)	10.5 (2)	1.3 (14)
30 - 39	0.3 (1)	2.2 (4)	1.6 (2)	5 (3)	7.6 (1)	1.5 (11)
40 - 49	1.5 (3)	1.1 (1)	0 (0)	8 (2)	0 (0)	1.6 (6)
50 - 59	1.2 (2)	0 (0)	2.7 (1)	3.8 (1)	0 (0)	1.3 (4)
≥ 60	1.3 (2)	2.5 (2)	3.3 (2)	11.1 (2)	11.1 (1)	2.8 (9)
Total	0.7 (14)	1.2 (11)	1.1 (8)	4.2 (14)	3.8 (4)	1.2 (51)
Male:						
≤ 9	0.5 (1)	2.4 (3)	4.2 (4)	2.4 (2)	0 (0)	1.9 (10)
10 - 19	0.9 (3)	2.3 (4)	3.1 (4)	4.6 (3)	3.4 (1)	2.0 (15)
20 - 29	0.6 (2)	1.2 (2)	0 (0)	0 (0)	7.1 (1)	0.8 (5)
30 - 39	0.3 (1)	2.2 (3)	1.0 (1)	2.3 (1)	0 (0)	1.0 (6)
40 - 49	0 (0)	1.2 (1)	1.5 (1)	3.8 (1)	0 (0)	0.8 (3)
50 - 59	0 (0)	0 (0)	0 (0)	0 (0)	14.2 (1)	0.4 (1)
≥ 60	1.2 (2)	2.3 (2)	1.8 (1)	0 (0)	14.2 (1)	1.8 (6)
Total	0.5 (9)	1.8 (15)	1.9 (11)	2.3 (7)	4 (4)	1.3 (46)

Numerals in parentheses denote number of cases

Table VI. Prevalence of liver enlargement per 100 people without any arsenical skin lesion by age group and arsenic level in water

Age group (yr)	Arsenic level in water (µg/l)					
	< 50	50-199	200-499	500-799	≥ 800	Total
Female:						
≤ 9	4.3 (7)	7.4 (6)	8.7 (9)	5.7 (4)	12.5 (3)	6.6 (29)
10 - 19	1.0 (4)	3.6 (6)	7.6 (12)	5.8 (4)	26.0 (6)	4.1 (32)
20 - 29	2.7 (15)	4.3 (11)	6.8 (11)	7.6 (5)	0 (0)	4.0 (42)
30 - 39	2.7 (9)	5 (9)	4.0 (5)	15 (9)	7.6 (1)	4.6 (33)
40 - 49	3.0 (6)	13.7 (12)	3.5 (2)	8 (2)	22.2 (2)	6.4 (24)
50 - 59	3.0 (5)	8.8 (6)	8.1 (3)	34.6 (9)	0 (0)	7.6 (23)
≥ 60	3.3 (5)	10 (8)	6.6 (4)	0 (0)	11.1 (1)	5.6 (18)
Total	2.6 (51)	6.3 (58)	6.6 (46)	9.9 (33)	12.6 (13)	5.0 (201)
Male:						
≤ 9	3.1 (6)	14.4 (18)	12.6 (12)	12.1 (10)	9.0 (2)	9.3 (48)
10 - 19	4.2 (14)	4.1 (7)	3.9 (5)	13.8 (9)	17.2 (5)	5.5 (40)
20 - 29	4.4 (13)	3.0 (5)	5.3 (5)	14.8 (7)	14.2 (2)	5.2 (32)
30 - 39	1.4 (4)	5.9 (8)	8.4 (8)	13.9 (6)	30 (3)	5.2 (29)
40 - 49	2.1 (4)	9.6 (8)	1.5 (1)	7.6 (2)	18.1 (2)	4.6 (17)
50 - 59	1.8 (2)	10.9 (7)	8.5 (3)	17.6 (3)	28.5 (2)	7.2 (17)
≥ 60	3.0 (5)	7.1 (6)	10.9 (6)	0 (0)	28.5 (2)	5.8 (19)
Total	3.1 (48)	7.1 (59)	7.0 (40)	12.5 (37)	18 (18)	6.0 (202)

Numeral in parentheses denote number of cases

Table VIII. Prevalence odds ratio (POR) for some systemic manifestations in people without any skin lesion comparing those exposed to arsenic ≥500 µg/l to participants exposed to arsenic <50 µg/l

	Females			Males		
	Cases exposed to > 500 µg/l	POR	95% CI	Cases exposed to > 500 µg/l	POR	95% CI
Weakness	38	5.48	3.4- 8.8	19	5.24	2.6-10.4
Anaemia	56	3.85	2.6-5.5	20	2.41	1.3-4.2
Chronic lung disease	35	1.76	1.1-2.6	43	0.93	0.65-1.3
Chronic diarrhoea	18	5.49	2.7-10.9	11	4.97	2.0-12.0
Hepatomegaly	46	4.34	2.8-6.5	55	5.13	3.4-7.6

found to be significantly high even in those without skin lesion[22]. In Chile, differences in respiratory disease were reported in school children with skin lesion compared to those without the lesions. Chronic lung disease like chronic cough was found among 38.8 per cent of 144 subjects with abnormal skin lesion compared with 3 per cent of 36 subjects with normal skin in a study among a cohort 180 residents of Antofagasta Chile[19].

The detection of arsenicosis cases is the cornerstone for case management and reporting for surveillance in an arsenic exposed population. In the recommended case definition algorithm of WHO[7] two major diagnostic criteria have been considered: (*i*) the presence of pigmentary and keratotic skin lesion; and (*ii*) evidence of exposure of elevated levels of arsenic established by history of intake of arsenic contaminated water or by raised arsenic level in hair and nails. The present findings highlighted that systemic manifestations like chronic lung disease, chronic diarrhoea, hepatomegaly, *etc.,* could also occur in arsenic exposed people in absence of skin lesions in significantly higher number of cases compared to non exposed population. Though these systemic manifestations are non specific and may be unrelated to arsenic, it is worthwhile to include people with systemic manifestations with evidence of arsenic exposure as suspected cases of arsenicosis. These cases need to be followed up for a prolonged period for detection of arsenical skin lesion and cancer on a later date.

The present cross-sectional study had certain limitations. It was an exploratory study and arsenic exposure was based on water arsenic report. No analysis of biological samples like hair, nail or urine could be carried out to substantiate arsenic exposure in body. A major strength of this study was that it was the first large population-based study with individual arsenic exposure data, which can provide critical information to characterize the exposure-response relationship with systemic manifestations in absence of dermatological lesions. The study showed an increase in proportion of both female and male patients suffering from weakness, anaemia, chronic lung disease, chronic diarrhoea and hepatomegaly with increase in concentration of arsenic in drinking water and this followed a dose-response relationship.

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