Review Article

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Chronic arsenic toxicity & human health

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Chronic arsenic toxicity (arsenicosis) due to drinking of arsenic contaminated ground water is a major environmental health hazard throughout the world including India. A lot of new information is emerging from extensive research on health effects of chronic arsenic toxicity (CAT) in humans during the last two decades. Available literature has been reviewed to highlight the problem including its malignancies. Pigmentation and keratosis are the specific skin lesions characteristics of CAT. CAT also produces various systemic manifestations over and above skin lesions, important ones being chronic lung disease like chronic bronchitis, chronic obstructive pulmonary disease and bronchiectasis, liver disease like non-cirrhotic portal fibrosis and other diseases like polyneuropathy, peripheral vascular disease, hypertension and ischeamic heart disease, diabetes mellitus, non-pitting oedema of feet/hands, weakness and anaemia. Cancer of skin, lung and urinary bladder are important cancers associated with chronic arsenic toxicity. Stoppage of drinking of arsenic contaminated water is the main stay in the management of arsenicosis as specific chelation therapy has limited value. Early skin cancer, detectable by regular active surveillance, is curable. In addition to dermatological features, CAT produces protean clinical manifestations. Treatment of arsenicosis is unsatisfactory and is mostly symtomatic.

Key words Arsenical neuropathy - arsenicosis - chronic arsenic toxicity - COPD - keratosis - pigmentation - treatment of arsenicosis

Introduction

Arsenic, a metalloid, occurs naturally, being the twentieth most abundant element in earth's crust and is a component of more than 245 minerals. The inorganic forms consisting mostly of arsenite and arsenate compounds are toxic to human health. Humans are exposed to arsenic primarily from air, food and water. Drinking water may be contaminated with arsenic from arsenical pesticide, natural mineral deposits or improperly disposed arsenical chemicals. However, elevated arsenic level in drinking water is the major cause of arsenic toxicity in the world. Reports of arsenic contamination in water are available from more than 30 countries in the world[1]. However, the major regions affected are in the river basin of the Ganga, Brahmaputra and Meghna in India and Bangladesh with an estimated 25 million people in Bangladesh and 6 million people in West Bengal, India exposed to arsenic contaminated ground water[1]. In India, though cases of arsenic toxicity including liver fibrosis due to drinking of arsenic contaminated water were reported from Chandigarh in early 1978[2], occurrence of large number of cases of arsenic induced skin lesions were reported from Kolkata, West Bengal in 1984[3]. Since then incidences

of chronic arsenic toxicity have been reported in the most States adjoining the upper, middle and lower Ganga and Brahmaputra plain. Arsenic contamination has been found in the States of Bihar, Uttar Pradesh, Jharkhand, Assam, Chhattisgarh and Andhra Pradesh[4,5].

Chronic arsenic toxicity (Arsenicosis)

Human health effects of chronic arsenic toxicity (CAT) are designated by the term arsenicosis which was first coined by our group[6] and later used by WHO[7] to imply a chronic disease caused by prolonged exposure in humans to arsenic. Previously the condition was described as arseniasis, arsenism, arsenicism, *etc*. Most of the reports of chronic arsenic exposure in man focus attention on skin manifestations because of their diagnostic specificity. However, data derived from population based studies, clinical case series and reports relating to intake of inorganic arsenic in drinking water, medications or occupational and environmental exposure, show that chronic arsenic exposure adversely affects multi organ systems of human body. The symptoms of chronic arsenic toxicity (arsenicosis) are insidious in onset and are dependent on the magnitude of the dose and duration of its exposure. There is a wide variation of occurrence of symptoms in an arsenic exposed population. All members of an affected family do not show clinical symptoms, the reason for such variation of disease expression is an enigma.

Skin manifestations

Pigmentation and keratosis are the specific skin lesions characteristic of chronic arsenic toxicity. The pigmentation of CAT commonly appears as a finely freckled, "raindrop" pattern that is particularly pronounced on the trunk and extremities distributed bilaterally symmetrically. The raindrop appearance results from the presence of numerous rounded hyperpigmented macules widely dispersed in the body (Fig. 1). Pigmentation might also involve mucous membranes such as undersurface of tongue or buccal mucosa. Other patterns include diffuse hyperpigmentation, localized patchy pigmentation, and leucomelanosis, in which the hypopigmented macules take on a spotty white appearance (Fig. 2). Leucomelanosis appears to occur in an arsenicosis patient following stoppage of drinking arsenic contaminated water for some duration[8-10].

Arsenical keratosis appears as diffuse thickening involving palms and soles, alone or in combination with nodules usually symmetrically distributed. The nodular forms are encountered most frequently on the thenar and lateral borders of palms, on roots or lateral surfaces of fingers and soles, heels and toes of feet. Such small nodules may coalesce to form large verrucous lesions (Fig. 3). The nodular form may also occur in the dorsum of the hands and feet and other parts of the body (Fig. 4). In severe cases, cracks and fissures may be seen in the soles. Keratosis is further subdivided into mild, moderate and severe. Mild form appears as slight thickening or minute papules (less than 2 mm) in the palms and soles, often associated with a grit-like texture, which may be primarily detectable by palpation. Moderate forms are multiple raised keratotic lesions (2-5 mm) while severe forms are large discreate or confluent elevations (>5 mm) on palms and soles, with nodular, wart-like or horny appearance[7,10]. Histological examination of the lesions typically reveals hyperkeratosis with or without parakeratosis, acanthosis, and enlargement of the rete

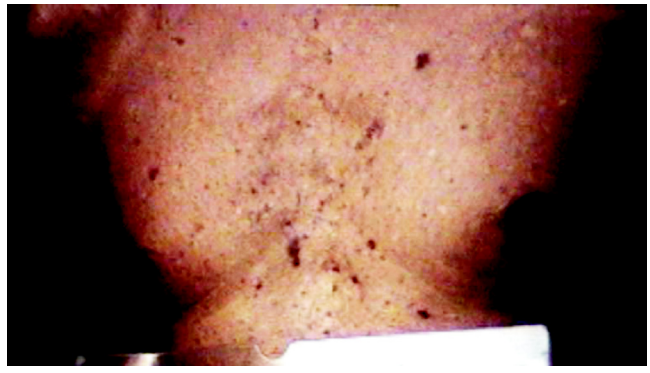

Fig. 1. Arsenical pigmentation (spotty rain drop like) affecting bilaterally over the front of the chest.

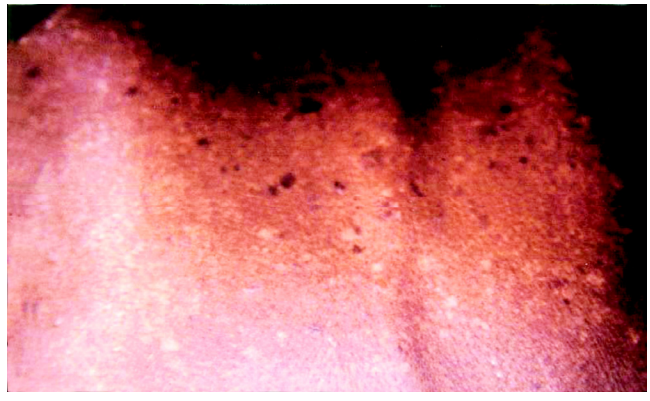

Fig. 2. Arsenical leucomelanosis (spotty depigmentation) involving both the thigh.

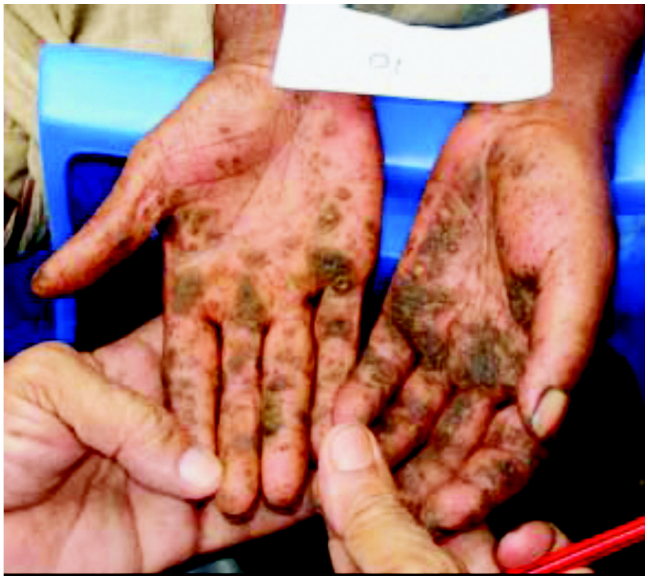

Fig. 3. Arsenical keratosis (nodular and confluent thickening) affecting both palm.

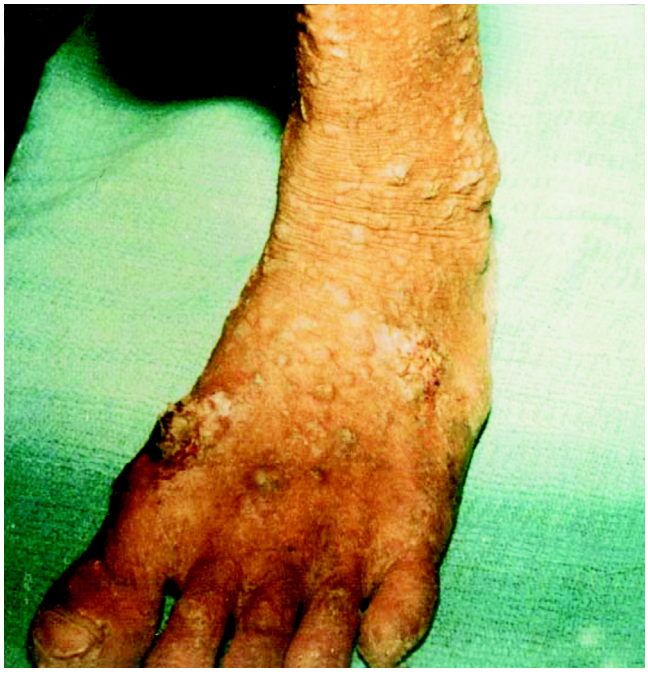

Fig. 4. Arsenical nodular keratosis involving dorsum of foot with skin cancer.

ridges. In some cases, there might be evidence of cellular atypia, mitotic figure, in large vacuolated epidermal cells[11].

To ascertain the prevalence of keratosis and pigmentation in relation to arsenic exposure, first population based survey was carried out on 7683 participants (4093 female and 3590 male) in West Bengal with individual arsenic exposure data[9]. Arsenic content of water source of the participants ranged from BDL (below detection limit) to 3.4 mg/l, however over 80 per cent of participants consumed water with arsenic level <0.5 mg/l. The age-adjusted prevalence of keratosis and pigmentation was strongly related to water arsenic levels, rising from zero and 0.3 in the lowest exposure level (<0.05 mg/l), to 8.3 and 11.5 per 100 respectively for females drinking water containing >0.8 mg/l, and increasing from 0.2 and 0.4 per 100 in the lowest exposure category to 10.7 and 22.7 per 100 respectively for males in the highest exposure level (>0.8 mg/l). Calculation by dose per body weight showed that men had roughly two to three times the prevalence of both keratosis and pigmentation compared to women apparently ingesting the same dose of arsenic from drinking water. Subjects who were below 80 per cent of the standard body weight for their age and sex had a 1.6 fold increase in the prevalence of keratosis suggesting that malnutrition may play some role in increasing susceptibility. However, the survey examined only the participants' primary current drinking water source. Results of a nested case control study using detailed lifetime (at least 20 yr) exposure assessment having low dose of arsenic exposure (<0.5 mg/l) among the above mentioned study population were also available[12]. The exposure assessment incorporated arsenic concentration data from current and past water sources used in households and work sites. The lowest peak arsenic ingested by a confirmed case was 0.115 mg/l. Strong dose response gradients with both peak and average arsenic water concentrations were also observed[12]. In another cross-sectional study, conduced in Bangladesh, 430 out of 1,481 subjects aged ≥ 30 yr and drinking arsenic contaminated water were found to have arsenical skin lesions. Arsenic water concentrations ranged from 0.01 to 2.04 mg/l and the crude overall prevalence rate for skin lesions was 29 per cent. This study also showed a higher prevalence rate of arsenical skin lesions in males than females with clear dose-response relationship[13].

Systemic manifestations

Chronic arsenic toxicity produces various systemic manifestations over and above skin lesions. This was evident from the report of the clinical features in 156 cases chronically drinking arsenic-contaminated water in West Bengal, India (Table)[14].

Table. Clinical features of 156 cases of chronic arsenicosis studied in West Bengal, India

Symptoms	No. of cases	Signs	No. of cases
Weakness	110 (70.5)	Pigmentation	156 (100.0)
Headache	32 (20.5)	Keratosis	96 (61.5)
Burning of the eyes	69 (44.2)	Anaemia	74 (47.4)
Nausea	17 (10.9)	Hepatomegaly	120 (76.9)
Pain in the abdomen	60 (38.4)	Splenomegaly	49 (31.4)
- epigastric	39 (25.0)	Ascites	5 (3.0)
- paraumbilical	21 (13.4)	Pedal oedema	18 (11.5)
Diarrhoea	51 (32.6)	Sign of lung disease	45 (28.8)
Cough	89 (57.0)	Sign of polyneuropathy	21 (13.4)
- with expectoration	53 (33.9)		
- without expectoration	36 (23.1)		
Haemoptysis	8 (5.1)		
Dyspnoea	37 (23.7)		
Paresthesia	74 (47.4)		

Source: Ref 14
Figures in parentheses are percentage values

Respiratory disease

Initial report of non malignant lung disease was available from a study of 180 residents of Antofagasta, Chile, exposed to drinking water containing arsenic (0.8 mg/l). About 38 per cent of 144 subjects with abnormal skin pigmentation complained of chronic cough, compared with 3.1 per cent of 36 subjects with normal skin[15]. Symptoms of chronic lung disease were present in 89 (57%) out of 156 cases of chronic arsenic toxicity caused by drinking arsenic contaminated water in West Bengal[14]. Lung function tests carried out on 17 patients showed features of restrictive lung disease in 9 (53%) and combined obstructive and restrictive lung disease in 7 (41%) cases[14].

To ascertain the relation of chronic arsenic exposure on occurrence of lung disease, an analysis of data of cross-sectional epidemiological survey of non smokers (6,864 participants) was carried out in West Bengal. Study subjects included those who had arsenic associated skin lesion and who were also highly exposed at the time of the survey (arsenic water concentration ≥0.5 mg/l). Individuals with normal skin and low arsenic water concentration (<0.05 mg/l) were used as the referent group. In participants with skin lesions, the age adjusted prevalence odds ratio (POR) estimates for cough, crepitations and shortness of breath for females were 7.8, 9.6 and 23.2 and for males 5, 6.9 and 3.7 respectively[16]. In an epidemiological study carried out on 218 non smokers (94 exposed to arsenic, 0.136 to 1 mg/l and 124 unexposed cases) in Bangladesh, the crude prevalence ratios for chronic bronchitis were found to be 1.6 (95% CI: 0.8-3.1) and 10.3 (95% CI: 2.4-43.1) for males and females respectively[17].

During 1998-2000, relation between lung function and exposure to arsenic in drinking water was ascertained in West Bengal among a cohort of 287 participants selected among study population who were exposed to low dose of arsenic exposure (up to 500 μg/l)[18]. The average forced expiratory volume in 1 second (FEV_1) adjusted for age, height and smoking was reduced by 256.2 ml (95% CI: 113.9, 398.4; P<0.001), and the average adjusted forced vital capacity (FVC) by 287.8 ml (95% CI: 134.9, 440.8; P<0.001) in men with skin lesions compared to those without skin lesion. An increase of 100 μg/l arsenic in drinking water was associated with a decrease in FEV_1 of 45 ml (95% CI: 6.2, 83.9, P=0.02) and in FVC of 41.4 ml (95% CI: 0.7, 83.5, P=0.05) in men. Women showed little evidence of lung function alteration. Thus, over and above respiratory symptoms, consumption of arsenic contaminated water in man was found to be associated with reduced, pulmonary function.

In a hospital-based study carried out on 29 cases of chronic arsenic toxicity with non malignant lung disease in Kolkata, West Bengal[19], obstructive lung disease was diagnosed in 17 (58.6%), interstitial lung disease in 9 (31.2%) and bronchiectasis in 3 (10%) cases. To ascertain the incidence of bronchiectasis in the population, 108 subjects with arsenic caused skin lesion and 150 subjects without skin lesion were studied in an arsenic endemic population in West Bengal[20,21]. The median highest arsenic in drinking water was 330 μg/l (SD= ±881 μg/l) in subjects with skin lesions compared to 28 μg/l (SD= ± 147 μg/l) in those without such lesions. Thirty eight study participants who reported at least two years of chronic cough underwent high-resolution computed tomography (HRCT). The mean bronchiectasis severity score was 3.4 (SD= ± 3.6) in the 27 participants with skin lesions and 0.9 (SD = ± 1.6) in the 11 participants without these lesions (controls). In subjects who reported chronic cough, HRCT evidence of bronchiectasis was found in 18 (67%) cases with skin lesion and in 3 (27%) controls[21]. Adjusted odds ratio was found to be 10.1 (95% CI=2.7-37.1). This study showed that drinking of high arsenic contaminated water was associated with increased incidence of bronchiectasis in man.

Many other investigators also reported chronic respiratory disease in the form of chronic cough or chronic bronchitis due to prolonged drinking of arsenic contaminated water[22-24].

Gastrointestinal disease

Symptoms of dyspepsia were observed in 60 out of 156 (38.4%) cases of chronic arsenic toxicity studied

in West Bengal[14]. However, in an epidemiological study carried out in the affected population there was no difference in the incidence of pain abdomen among people drinking arsenic contaminated water and control population (27.84 vs 31.81%)[25]. Gastroenteritis was reported in a study of 1447 cases of chronic arsenicosis caused by drinking arsenic contaminated water (0.05-1.8 mg/l) in the Inner Mongolian Autonomous region of China[23]. Many investigators variously reported symptoms like nausea, diarrhoea, anorexia and abdominal pain in cases of chronic arsenic toxicity[6,15,26-28].

Liver disease

Many workers have reported, earlier, cases of liver damage following treatment of patients with arsenic as Fowler's solution[29-31]. All these patients developed features of portal hypertension with signs of liver fibrosis. Typical cutaneous signs of long-term arsenic exposure were also observed in some of the patients. There have also been case reports of liver cirrhosis following medication with inorganic arsenic compounds[32,33].

Portal hypertension associated with portal fibrosis was reported in nine patients who were found to have high arsenic level in their liver in Chandigarh, India. Two of those patients had been found to be drinking arsenic contaminated water (0.549 and 0.360 mg/l)[2]. Hepatomegaly was found in 62 out of 67 members of families who drank arsenic contaminated water (0.2-2 mg/l) in West Bengal while it was found in only six out of 96 people who took safe water in the same area[6]. Thirteen of those arsenic exposed patients who had hepatomegaly were further investigated in a hospital. All showed various degrees of portal zone expansion and fibrosis on liver histology (Fig.5). Four out of five patients who had splenomegaly showed evidence of increased intrasplenic pressure (30-36 cm salne) suggesting portal hypertension. Splenoportography done in those cases showed evidence of intrahepatic portal vein obstruction. Although routine liver function tests were normal in all those thirteen cases investigated, the bromsulphthalein retention test, done in three patients, was found to be abnormal. The arsenic level in liver tissue (estimated by Neutron activation analysis) was found to be elevated in 10 out of those 13 cases (As levels: Cases- 1.6 ± 1.66 mg/kg; control- 0.10 ± 0.04 mg/kg)[6]. In a subsequent report from the same hospital hepatomegaly was found in 190 out of 248 case of chronic arsenicosis investigated. Evidence of portal fibrosis on liver histology was found in 63 out of 69 cases of hepatomegaly who were biopsied. Liver functions tests carried out in 93 such patients showed evidence of elevation of ALT, AST and ALP in 25.8, 6.3 and 29 per cent of cases respectively. Serum globulin was found to be high (>3.5 g/dl) in 19 (20.7%) cases[34].

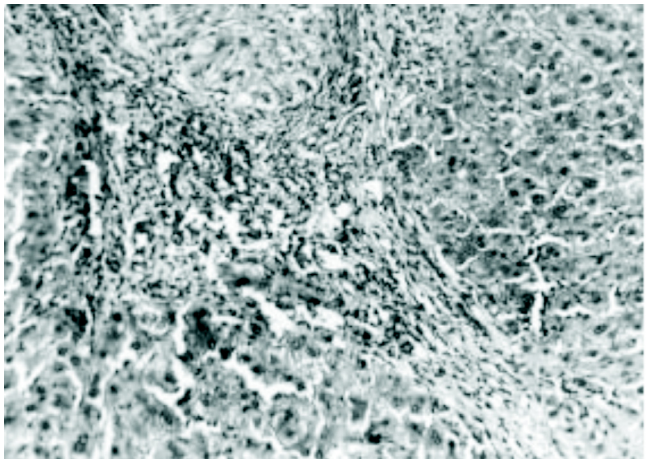

Fig. 5. Severe fibrosis of liver with expanded portal zone containing leash of vessels in a patient of arsenicosis and non cirrhotic portal fibrosis.

In another epidemiological study carried out in West Bengal with 3467 and 4216 people, with arsenic level below and above 0.05 mg/l, respectively in drinking water, prevalence of hepatomegaly was significantly higher in arsenic exposed people (10.2%) compared to controls (2.99%, $P<0.001$). The incidence of hepatomegaly was found to have a linear relationship proportional to increasing exposure of arsenic in drinking water in both sexes ($P<0.001$)[25]. Liver enlargement was also reported following drinking of arsenic contaminated water by other workers[8,22-24].

All these studies show that prolong drinking of arsenic contaminated water is associated with hepatomegaly, predominant lesion being hepatic fibrosis.

Cardiovascular disease

Black foot disease, (BFD) a form of peripheral vascular disease, has been reported to be one of the important complication of chronic arsenic toxicity in Taiwan. It is a unique peripheral arterial disease characterized by the severe systemic arteriosclerosis as well as dry gangrene and spontaneous amputations of affected extremities at end stages. Histologically, BFD can be divided into two reaction groups, arteriosclerosis obliterans and thromboangitis obliterans, particularly affecting small vessels[35]. Clinically the disease begins with patients' subjective complaints of coldness or numbness in the extremities (usually in the feet) and intermittent claudication, progressing over the course

of several years to ulceraton, gangrene, and spontaneous amputation[36]. The prevalence of BFD has been reported to be 8.9 per 1000 among 40,421 inhabitants studied in Taiwan[37]. Comparable peripheral vascular disorders with varying degrees of severity including Raynaud's syndrome and acrocyanosis have also been reported among people drinking arsenic contaminated water by others[14,15,23,24,33,38]. It needs to be emphasized that there are differences in the prevalence of peripheral vascular disease causing gangrene and amputation among different population exposed to arsenic, the incidence being high in Taiwan, while low in Chile, India and Bangladesh while there is no report from Maxico and Argentina[39].

An epidemiological study reported an increased prevalence of hypertension among residents in the endemic area of black foot disease and a dose-response relationship between ingested inorganic arsenic and prevalence of hypertension[40]. The investigators studied a total of 382 men and 516 women residing in arsenic hyperendemic areas in Taiwan. They observed 1.5 fold increase in age and sex adjusted prevalence of hypertension compared with residents in nonendemic areas. The higher the cumulative arsenic exposure the higher was the prevalence of hypertension. The dose-response relation remained significant after adjustment for age, sex, diabetes mellitus, proteinuria, body mass index and serum triglyceride level. Increased prevalence of hypertension was also reported in 6.2 per cent patients affected with arsenic induced skin lesions (144) compared to none without skin lesion (36) in Antafagesta, Chile[15]. Association of cumulative arsenic exposure in drinking water was also found to be associated with increased risk of hypertension in a study of 1595 people in Bangladesh[41].

Mortality rates from ischaemic heart disease (IHD) with endemic arsenicosis (from 1973 through 1986) were correlated with their association with arsenic level in drinking water among residents of 60 villages in Taiwan[42]. Based on 1355915 person years and 217 IHD deaths, the cumulative IHD mortalities from birth to age 79 yr were 3.4, 3.5, 4.7 and 6.6 per cent, respectively, for residents who lived in villages in which the median arsenic concentrations in drinking water were <0.1, 0.1 to 0.34, 0.35 to 0.59 and ≥ 0.6 mg/l. A cohort of 263 patients affected with BFD and 2293 non-BFD residents in the endemic area of arsenicosis were recruited and followed up for an average period of 5.0 yr. There was a monotonous biological gradient relationship between cumulative arsenic exposure through drinking artesian well water and IHD mortality. The relative risks were 2.5, 4.0, and 6.5 respectively, for those who had a cumulative arsenic exposure of 0.1 to 9.9, 10.0 to 19.9, and ≥ 20.0 mg/l years compared to those without the arsenic exposure after adjustment for age, sex, cigarette smoking, body mass index, serum cholesterol and triglyceride levels, and disease status for hypertension and diabetes through proportional hazards regression analysis.

Ingested inorganic arsenic has been related to an increased incidence of cardiovascular disease, especially ischaemic heart disease and has been reviewed extensively[10,39,43,44].

Diseases of nervous system

There are many reports on occurrence of peripheral neuropathy due to chronic exposure of arsenic through drinking water[8,23,24,27,45,46]. Peipheral neuritis charecterized by paresthesia (tingling, numbness, limb weakness, *etc.*) was present in 74 (47.4%) out of 156 patients of chronic arsenicosis due to drinking of arsenic contaminated water (0.5-14.2 mg/l) in West Bengal, India. Objective evaluation of neuronal involvement, done in 29 patients, showed abnormal electromyography (EMG) in 10 (30.8%) and altered nerve conduction velocity and EMG in 11 (38%) cases[47]. Abnormal EMG findings suggestive mostly of sensory neuropathy was reported in 10 out of 32 subjects exposed to drinking arsenic contaminated well water (range 0.06 to 1.4 mg/l) in Canada[48]. In another electrophysiological study carried out on 88 patients of arsenicosis in West Bengal, sensory neuropathy was found in 24 (27.3%), motor neuropathy in 13 (14.7%) and abnormal EMG in 5 (5.7%) cases[49].

Increased incidence of cerebrovascular disease has been reported by many in patients suffering from chronic arsenicosis[23,44,45]. In a cross-sectional study in Taiwan relationship between the prevalence of cerbrovascular disease and ingestion of inorganic arsenic in drinking water was investigated[50]. A total of 8102 men and women from 3901 households were recruited in this study. The status of cerebrovascular disease of study subjects was identified through home visit, personal interviews and by review of hospital medical records according to the WHO criteria. Information on consumption of well water, socio-demographic characteristics, cigarette smoking, and alcohol consumption habits, as well as personal and family history of disease, was also obtained. A significant dose-response relationship was observed between arsenic concentration in well water and prevalence of

cerebrovascular disease after adjustment for age, sex, hypertension, diabetes mellitus, cigarette smoking and alcohol consumption. The biological gradient was even more prominent for cerebral infarction, showing multivariate-adjusted odds ratios of 1.0, 3.4, 4.5 and 6.9, respectively, for those who consumed well water with an arsenic content of 0, 0.001 to 0.05, 0.051 to 0.299, and > 0.3 mg/l[50].

Peripheral neuritis, sleep disturbances, weakness and cognitive and memory impairment have been reported in residents of Byan College Station, Texas exposed to arsenic from air and water from arsenic trioxide used to produce defoliants from an Atochem plant[46]. Headache has been reported to occur in people drinking arsenic contaminated water in Mexico[27] and in West Bengal[14]. Irritability, lack of concentration, depression, sleep disorders, headache and vertigo were reported in arsenicosis people showing features of neuropathy in West Bengal[49].

Haematological effects

Haematological abnormalities have been reported in acute and chronic arsenic poisoning[10]. A characteristic pattern of anaemia, leucopaenia and thrombocytopaenia was found in 55 individuals exposed to arsenic in drinking water in Niigata Prefecture in Japan for approximately 5 years, half of the subjects having arsenical skin lesion[51]. In one study in West Bengal, anaemia was reported in all the 13 people exposed to arsenic contamiated ground water (0.2-2 mg/l)[6]. Further study in West Bengal on 156 people exposed to arsenic contaminated water (0.05-14.2 mg/l) showed incidence of anaemia in 47.4 per cent of cases[14]. However, no association of anaemia was found in people drinking well water (mean 0.22 mg/l) in Alaska[52] and in two towns of Utah (arsenic exposure 0.18 and 0.27 mg/l)[53].

Diabetes

A dose-response relation between cumulative arsenic exposure and prevalence of diabetes mellitus was observed in Taiwan following a study on 891 persons living in arsenic endemic areas. The status of diabetes mellitus was determined by an oral glucose tolerance test and a history of diabetes regularly treated with sulphonylurea or insulin. The relation remained significant after adjustment for age, sex, body mass index and activity level at work by a multiple logistic regression analysis giving a multivariate adjusted odds ratio of 6.61 and 10.05, respectively, for those who has a cumulative arsenic exposure of 0.1-15.0 and greater than 15.0 mg/l year compared with those who were unexposed[54].

Form Bangladesh significantly increased prevalence of diabetes mellitus was reported due to drinking arsenic contaminated water among subjects with keratosis compared with subjects who did not have such lesion. A significnat trend in risk between an approximate time-weighted arsenic expsoure and the prevalence of diabtes mellitus strenghened the possibility of a causal association[55]. However, the lack of a comprehensive, systematic long-term sampling of the water supplies in the study area is a limiation of the study because directly measured individual exposure data over time would have been desirable. However, these results suggest that CAT may induce diabetes mellitus in humans.

Pregnancy outcome

No conclusive information on pregnancy outcome and infant mortality in relation to arsenic levels in drinking water is available in literature as a few studies included individual assessment of arsenic concentrations in all water sources used during each pregnancy. In an ecological study carried out in Chile, stillbirths (rate ratio 1.7; 95% CI: 1.5, 1.9), neonatal and postneonatal infant mortality rates were found to be increased in the high arsenic exposure city of Antofagasta as compared with the low exposure city Valparaiso[56]. A study conducted in Bangladesh showed an increased risk for stillbirth for women with current arsenic levels of ≥100 μg/l, although the risk estimates were smaller (OR= 2.5; 95% CI: 1.5, 5.9). The authors further reported increased effects on spontaneous abortions (OR=2.5; 95% CI: 1.5, 4.4)[57]. However no information was available on arsenic exposure during pregnancy, and high exposure levels of 200 μg/l and more were not considered separately in this study. One earlier cross-sectional study from Bangladesh compared rates of spontaneous abortions, stillbirths and preterm delivery between 96 women in one village who were exposed to ≥100 μg/l arsenic to rates in 96 women in another village who were exposed to less than 20 μg/l, and showed two to three times higher rates among exposed women[58]. Both Bangladesh studies reported a relation to overall duration of women's exposure without taking into account exposure during the actual time period of pregnancy.

A retrospective study of pregnancy outcomes and infant mortality was conducted in West Bengal, India, among 202 married women selected from a source population of 7,683 between the years 2001 and 2003[59].

Reproductive histories were ascertained by structured interviews. Arsenic exposure during each pregnancy was assessed based on all water sources used, involving measurements from 409 wells. Odds ratios for spontaneous abortions, stillbirth, neonatal and infant mortality were estimated with logistic regressions based on the method of generalized estimating equations. High concentrations of arsenic ≥200 µg/l during pregnancy were associated with a six-fold increased risk for stillbirth after adjusting for potential confounders (odds ratios= 6.25; 95% confidence interval: 1.59, 24.6, *P*=0.009). Arsenic-related skin lesions were found in 12 women who had a substantially increased risk of stillbirth (OR=13.1, 95% CI: 3.17, 54.0, *P*=0.002). The odds ratio for neonatal death was 2.03 (95% CI: 0.57, 7.24). No association was found between arsenic exposure and spontaneous abortion (OR = 0.90; 95% CI: 0.36, 2.26) or overall infant mortality (OR =1.18, 95% CI: 0.38, 3.64). This study adds to the limited evidence that exposure to high concentrations of arsenic during pregnancy increases the risk of stillbirth. However, there was no indication of increased rates of spontaneous abortion and overall infant mortality[59].

Other effects

High incidences of weakness and fatigue have been reported in chronically arsenic exposed people following drinking arsenic contaminated water by many workers[6,8,14,25,26,46,60]. Conjunctival congestion and nonpitting oedema of the legs (Fig. 6) and hands have also been reported in patients of chronic arsenic toxicity in West Bengal and Bangaldesh[14,24,28,61].

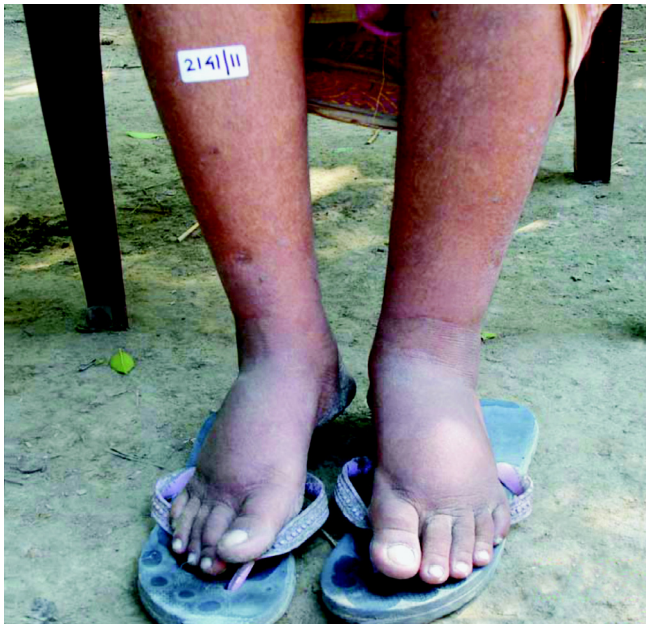

Fig. 6. Non pitting oedema of legs with thickening of the palm in a patient of arsenicosis.

Arsenicosis and cancer

The evidence of carcinogenicity in humans from exposure to arsenic is based on epidemiological studies of cancer in relation to arsenic in drinking water. The working group of International Agency for Research on Cancer[4] evaluated data from ecological studies, cohort studies and case-control studies from many countries and observed that arsenic was potentially carcinogenic for skin cancer. Malignant arsenical skin lesions may be Bowen's disease (intraepithelial carcinoma, or carcinoma *in situ*), basal cell carcinoma, or squamous cell carcinoma. Skin cancer might arise in the hyperkeratotic areas or might appear on nonkeratotic areas of the trunk, extremities, or hand. Bowen's disease appears as sharply demarcated round plaque or has an irregular polycyclic lenticular configuration. Frequently multiple lesions are seen (Fig. 7). The lesions are usually erythematous, pigmented, crustated, fissured and keratotic. Some may be nodular, ulcerated or eroded. The diameter of the lesions may vary from 0.8 to 3.5 cm[62,63].

Further there is increased risk of development of urinary bladder cancer and lung cancer due to chronic exposure to arsenic. When all the epidemiological data are considered for these two cancers, the findings could not be attributed to chance or confounding[4] and they are consistent, with strong associations found in populations with high exposure of arsenic[4]. There is evidence of dose-response relationships within exposed population. Increased risk of liver cancer has also been reported

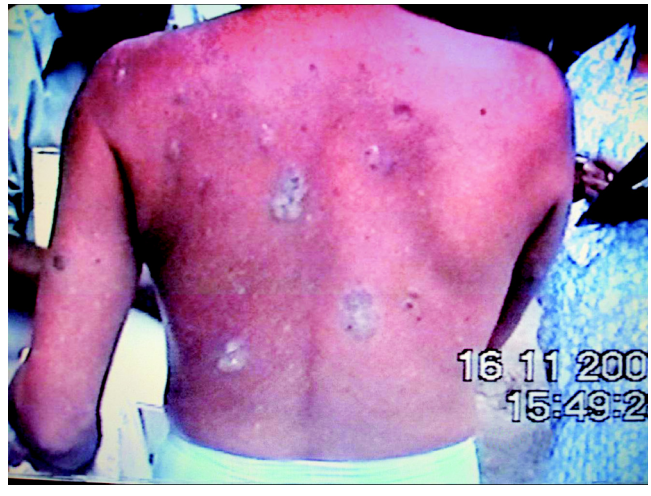

Fig. 7. Multiple Bowens disease in the back in a case of arsenicosis.

in several studies identified from death certificates. But there is limitation of interpretation of these findings because of questionable accuracy of the diagnosis of liver cancer on death certificates and potential confounding or modifying effects of hepatitis virus infection or other factors. Epidemiological studies in several countries involving population with high long-term exposure to arsenic found increased risks for kidney cancer also. Relative risk estimates for kidney cancer were generally lower than those for urinary bladder cancer, and no studies have reported dose-response relationships on the basis of individual exposure data. Excess mortality from prostate cancer was found in southwest Taiwan[4]. Inconsistent findings were reported for other cancers[4].

Diagnosis

Arsenicosis is defined as a chronic health condition arising from prolonged ingestion of arsenic above the safe dose for at least six months, usually manifested by characteristic skin lesions of melanosis and keratosis, occurring alone or in combination, with or without the involvement of internal organs[7]. Although chronic arsenic toxicity produces varied systemic manifestations as well as cancer of skin and different internal organs, dermal manifestations such as pigmentation and keratosis are diagnostic of chronic arsenicosis. For this reason field guide of diagnostic algorithm of arsenicosis[7] is based on presence or absence of characteristic dermatological manifestations of chronic arsenic toxicity. According to this field guide[7], a clinically confirmed case of arsenicosis is a "probable case with pigmentation and/or keratosis" in whom the presence of other arsenicosis simulating skin lesions has been ruled out by differential in-depth skin examination by either a trained dermatologist or an arsenic expert. A "clinically and laboratory confirmed case" is a "clinically confirmed case" in whom the arsenic test is also positive by the laboratory criteria recommended. Laboratory criteria for establishing exposure history of arsenicosis cases are: (*i*) consumption of drinking water with an arsenic concentration in excess of prevailing national standards for at least six months. (Country Standard in Asia Pacific Region is 0.05 mg/l while WHO Standard is 0.01 mg/l) [Indian standard of arsenic level for drinking water: According to Bureau of Indian Standard: 0.01 mg/l[5]; According to Rajiv Gandhi National drinking water Mission: 0.05 mg/l[5] as the "Maximal Permissible Limit"]; and (*ii*) an elevated concentration of arsenic in hair (> 1 mg/kg of hair) or in nail clippings (> 1.5 mg/kg of nail)[7].

Management of chronic arsenic toxicity

Chronic arsenicosis leads to irreversible damage in several vital organs, and arsenic is an established carcinogen. Though there is no significant morbidity of milder form of the disease, mortality is high in severe cases. Despite the magnitude of this potentially fatal toxicity, there is no effective therapy for this disease. Complications of moderate and severe form of arsenicosis may not be prevented even after remediation of the arsenic-contaminated water.

However people should be advised to stop drinking arsenic contaminated water or exposure to arsenic from any other source. To determine the effect of providing safe water to affected people, a cohort of 24 patients with chronic arsenicosis were re-examined after drinking arsenic-free water (<10 μg/l) for a period varying from 2 to 10 yr (13 patients 10 yr, 11 patients 2-5 yr) in West Bengal[64]. These people had been drinking arsenic-contaminated water (0.13-2.0 mg/l) for 4-15 yr. Partial improvement of pigmentation and keratosis were observed in 45 and 46 per cent of patients, respectively. However, liver enlargement was persistent in 86 per cent of cases. The most distressing observation was the new appearance of signs of chronic lung disease (cough, shortness of breath and chest signs) in 41.6 per cent of cases. There was a slight reduction of clinical symptoms of neuropathy[64]. Study reports are available on changes of severity of skin lesions amongst an affected cohort of arsenicosis patients in Southern Thailand where interventions to reduce arsenic contaminated water had been implemented. Over 10 year period, both regression and progression of lesions occurred, though the majority of the subjects followed up remained the same. Drinking predominantly arsenic free water increased the probability of regression in subjects with mild stage lesions but not in those with more advanced stage lesions. By contrast, a high arsenic content in the household well water, even though it was not used for drinking, decreased the probability of lesion regression among the subjects in more advanced stage but not among milder stage cases. Irrespective of initial stage a period of absence from the affected area increased the likelihood of lesion regression[65]. Another cohort follow up study was carried out on 1074 people (arsenic exposed people 623, control population 451) in 2000, five years after the original clinical examination done on the same population at South 24 Parganas, West Bengal. Out of 199 people with skin lesion among the arsenic exposed population who were consuming safe water during the previous 5 years, the skin lesions cleared or decreased in 49.7 per cent of

people. However, out of 306 people who did not have such lesions previously, new skin lesions appeared in 32 (10.5%)[66]. Skin lesions were reported to improve to some extent in cases of arsenicosis in Inner Mongolia, China, after drinking low arsenic containing water for one year. However, five years follow up study showed no more significant improvement of skin lesions, while the potential risk of arsenic induced cancers after cutting off high arsenic exposure was still uncertain and indefinite[67].

From the results of these studies it becomes apparent that significant improvement of mild and moderate dermatological manifestations occurs in many cases of arsenicosis after continuous drinking of arsenic free water. However, symptoms of severe keratosis and systemic manifestations of arsenicosis may persist in spite of stoppage of consumption of arsenic-contaminated water. Further, there remains the potential risk of arsenic induced cancer in these cases. Hence there is a need for an effective therapeutic intervention for the treatment of chronic arsenicosis.

Chelation therapy for chronic arsenic toxicity is thought to be the specific therapy for relief of systemic clinical manifestations and reduction of arsenic stores in the body, reducing subsequent cancer risk. A study evaluating the efficacy of specific chelation therapy with DMSA (dimercaptosuccinic acid) for patients suffering from chronic arsenic toxicity has not yielded better efficacy than control subjects treated with placebo[68]. But in another study, chelating agent DMPS (dimercapto propane sulphonate) demonstrated significant improvement of clinical score among drug treated cases compared to controls in a single blind placebo control trial. Increased urinary excretion of arsenic during the period of drug therapy was also demonstrated during the study[69]. However, the drug is costly, not available locally and reports of long-term clinical trial are not available. Therefore the drug could not be recommended currently, for routine use for chronic arsenocosis patients in India. Improvement of symptoms of arsenicosis patients in Bangladesh have been reported to occur following use of antioxidants like vitamin A, C and E[70]. However, no placebo controlled trial with the vitamins have been carried out nor the toxicity of their long-term use has been ascertained.

Supportive treatment could help in reducing many symptoms of these patients. Treatment in hospital with good nutritious diet has been found to reduce symptom score in subsets of placebo treated arsenicosis patients during the course of DMSA and DMPS trial[68,69].

Presently the most prevailing practice of symptomic treatment of keratosis is to apply locally 5-10 per cent of salicylic acid and 10-20 per cent urea based ointment on keratotic skin lesions[7]. Higher doses need further evaluation. Though specific treatment for chronic arsenic toxicity has not yet been fully established, supportive and symptomatic treatment could help in reducing many symptoms of the patients. Arsenic induced cancers could be cured if detected early. Hence a good cancer surveillance programme in chronic arsenic exposed population is essential for preventing cancer related deaths. Mass communication measures should be undertaken in the arsenic endemic areas highlighting that people should get their drinking water source tested for arsenic and stop its consumption if found contaminated.

In summary, predominant manifestation of chronic arsenic toxicity are skin lesions characterized by pigmentation and keratosis. However it produces protean systemic manifestation over and above skin lesions, important ones being chronic lung disease like chronic bronchitis, chronic obstructive pulmonary disease and bronchiectasis, liver disease like non cirrhotic portal fibrosis and other diseases like polyneuropathy, peripheral vascular disease, hypertension and ischeamic heart disease, diabetes mellitus, non-pitting edema of feet/ hands, weakness and anemia. Cancer of skin, lung and urinary bladder are important cancers associated with chronic arsenic toxicity.

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