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Environmental Exposure and Hazards of Arsenic: A Review

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Abstract **- Arsenic contamination in groundwater in the Padma-Meghna fluvial plains in Bangladesh and Ganga-Brahmaputra fluvial plains in India and its consequences to the human health have been described as one of the world's largest natural groundwater catastrophes to the manhood. In India, seven states namely: Jharkhand, Bihar, Uttar Pradesh, and West Bengal in the flood plain of the Ganga River, Manipur and Assam in the flood plain of the Brahamaputra and Imphal rivers and Rajnandgaon community in Chhattisgarh state have so far been reported pretentious by Arsenic contamination in groundwater exceeding the permissible limit of 10 µg/L. People in these affected states have frequently been exposed to drinking Arsenic contaminated hand tube-well water. Arsenic groundwater contamination has far-reaching consequences including its consumption through food chain which are in the form of social disorders, health hazards and socio-economic dissolution besides its sprawling with movement, and exploitation of groundwater. Arsenic contamination is implicit to be of geogenic origin released from soil under conditions promisingto dissolution of Arsenic from solid phase on soil grains to liquid phase in water, and percolation of fertilizer residues might have played a modifying role in its further exaggeration. Despite a number of remedial and protective measures, the spread of Arsenic contamination in groundwater continued to grow and more new areas were also added to the list of contaminated areas. The problem resolving issues, thus, seemed to be incomplete and insufficient, which need to be supported by strategic scientific support.**

Key words: ***Arsenicosis, Chronic Arsenic Toxicity, Keratosis, Pigmentation, Acute Toxicity, Chronic Toxicity, Melanosis, Ground Water, Permissible Limit.***

INTRODUCTION

Arsenic is an element with symbol As with atomic number 30 occurs in many minerals in pure as well as in conjugated form. Arsenic was first documented in 1250 by Albertus Magnus [1]. Arsenic is a naturally occurring metalloid, 20th most abundant element in earth's crust and is a component of 245 minerals, exist in many allotropes but industrial application is mostly for its gray form. Main application of metallic Arsenic is to strengthen the alloys of copper which is mainly used in car batteries. As compounds in general and Arsenic trioxide in particular are used in pesticide production, herbicide and insecticide preparation, however this kind of application for arsenic is declining day by day [2].

Arsenate and Arsenite are its inorganic forms which are toxic to human health. Exposure of Arsenic to human beings can be from food, air and water. Natural mineral deposits, arsenical pesticides and improper dispose of arsenical compounds may contaminate drinking water. However Arsenic toxicity in the world is due to elevated Arsenic levels in drinking water. About 30 countries around the world have been reported for As contamination in their waters [3]. River basin of Ganga, Maghna and Brahmaputra are the major regions affected due to Arsenic contamination in India and Bangladesh with an estimate of six million people in west-Bengal and over 25 million in Bangladesh. Exposure to Indian population is mainly through ground water. In early 1978 [4]. liver fibrosis was reported from Chandigarh India due to consumption of Arsenic contaminated drinking water, similarly Arsenic induced skin lesions were reported from Kolkata West-Bengal in 1984 [5] and since then causes of Chronic Arsenic toxicity have been well reported from states adjoining Ganga and Brahmaputra plain like Utter Pradesh, Bihar, Assam, Jharkhand, Andhra Pradesh and Chhattisgarh [6,7]. In this review study has been finalized in concise form to compile important information in order to suggest remedial measures of arsenic in the context of India.

HISTORY AND USE

Arsenic has been derived from a Latin word "arsenicum". Since ancient times, arsenic sulphide (orpiment, realgar) and oxides have been known and used [8]. Due to ill-defined symptoms of Arsenic poisoning, it was mostly used for murder until Marsh test (a sensitive chemical test which confirms arsenic presence) was developed. Arsenic has been called the king of poisons because of its potency and discreetness [9]. In Victorian period, mixture of arsenic, (white arsenic or arsenic trioxide) vinegar and chalk was given to women in order to improve their face complexion and to make their skin paler to express that they are not field workers. Women used to rub arsenic on the faces and arms to improve their complexion. However, 20 deaths occurred due to accidental adulteration of As in food stuffs in UK in 1858 [10].

Chemistry

Arsenic when heated with air, gets oxidized to arsenic trioxide, the fumes produced in this reaction possess an odour resembling garlic. This odour can be detected by striking arsenide minerals such as arsenopyrite with a

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hammer. Upon heating at atmospheric pressure, arsenic sublimes and directly gets converted into gaseous form without intermediate liquid state at 887K (614°C) [11]. On reaction with concentrated nitric acid, dilute nitric acid and concentrated H_2SO_4 arsenic produces arsenic acid, arsenous acid and arsenic trioxide, respectively [12].

SOURCE OF EXPOSURE

Arsenic exposure can occur through several sources such as, natural source, industrial source and accidental or administered source. Unintentional consumption of arsenic by children and suicidal attempts by adults reflects the rare cases of acute arsenic poisoning [13].

Arsenic containing insecticides, herbicides and rodenticides are the typical self- administration sources of arsenic. Children are more vulnerable to accidental exposures. Chronic exposures are often most challenging diagnostically. Around the world, exposure of arsenic has been reported via water, air, food and beverage. Due to over withdrawal of ground water for irrigation purpose and other industrial operations, exposure via drinking water is increasing at an alarming rate. Environmental exposure and occupational health problems can result from frequent presence of commercial arsenicals. Under several occupational conditions, arsine gas exposure can also result in environmental health hazard. Arsine being colourless, odourless, tasteless and non- irritating gas causes a rapid damage to red blood cells and can also lead to kidney failure which can prove fatal if proper therapy is not given at proper time. Numerous cases of arsine poisoning have occurred due to the use of crude metals and acids containing arsenic as an impurity [14]. Inhalation and ingestion are the two main routes of arsenic absorption. Some degree of skin absorption of trivalent arsenic oxide may also occur as it is more lipid – soluble than penta-valent form [15]. Symptoms caused by acute gastrointestinal irritation will be more if the exposure is via ingestion as the ingested arsenic has a very short half-life than inhaled arsenic due to extremely rapid biotransformation in the liver [16]. If the exposure is through inhalation then respiratory irritation will be the primary determinant of early symptoms. However, after arsenic absorption, the vascular circulation can lead to a variety of symptoms and ultimately may result in possible organ damages. Ingestion, inhalation and skin absorption are the main exposure routes to human body. About 95% of ingested trivalent arsenic gets absorbed in gastro intestinal tract, whereby it gets distributed in various organs like lungs, kidney, liver and skin [17]. About 90-95% of arsenic gets located in erythrocytes after being absorbed through lungs and gastro- intestinal tract and then binds with globin of hemoglobin and is transported to other parts of the body [18]. Excretion of 70% of arsenic occurs through urine. In the body, liver converts most of the absorbed arsenic into its less toxic methylated form which is then effectively excreted in urine. Compared with rate for other organs in the body, the rate of decline in arsenic in the skin seems to be very low [19].

Arsenic poisoning (Acute)

Acute arsenic toxicity symptoms occur usually after 30 minutes of ingestion but may delay if arsenic is consumed with food. At initial stage, patient may feel metallic taste with garlicky odour and may also feel difficulty in swallowing. Initial clinical symptoms of acute arsenic intoxication can be muscle pain, weakness associated with flusking skin. Severe symptoms may be nausea, vomiting, abdominal pain and profuse diarrhea. Arsenic toxicity badly affects mucosal vascular supply which leads to mucosal vesicle formation and tissue fragment sloughing. Patient may complain of numbness in feet and hands, muscle cramps and strong thirst. On extreme intoxication, it leads to coldness of skin and can also result in circulatory collapse along with kidney damage with decline in urine output. Confusion and drowsiness are often seen and finally leads to seizures, coma and death. Multisystem organ damage may occur after fallowing the gastrointestinal phase. In first 24 hours, if death doesn't occur from irreversible circulatory insufficiency, then it can result in renal or hepatic failure over the next few days of intoxication. Cardiac manifestations can be acute cardiomyopathy, electrocardiographic changes and sub-endocardial hemorrhages [20].

Arsenic poisoning (chronic)

Chronic arsenic poisoning is highly insidious in nature; often involve numerous hospital admissions before going for correct diagnosis. Skin, liver, lungs and blood system manifestations can occur in most of the chronic arsenic toxicity cases [21]. First diagnosis was confirmed in west Bengal and Bangladesh by K.C Sahu at school of Tropical medicine Calcutta in December 1984 [28]. The skin pigmentation of the patient looks patchy and has been given a poetic description of "raindrops on a dusty roa" [22]. Negative effects of chronic arsenic toxicity are termed as arsenicosis to describe the chronic disease caused by prolonged exposure of arsenic to human beings. Most of the chronic arsenic exposure reports in human body focus attention on skin manifestations due to their diagnostic specificity. However, data derived from clinical case studies, population base studies related to consumption of inorganic arsenic in drinking water occupational and environmental exposure depicted that multi organ system of the humans get badly or adversely affected by chronic arsenic exposure. Symptoms of arsenicosis are very complex in onset and are mainly dependent on the dose magnitude and duration of exposure. In an arsenic exposed population, symptom occurrence shows a remarkable variation. All the members of affected family don't show same symptoms, the reason for this kind of distinction in disease expression is an enigma.

Dermal Effects

Specific skin lesions like pigmentation and keratosis are characteristic of chronic arsenic toxicity. Chronic arsenic toxicity pigmentation generally appears as a very fine freckled "raindrop"pattern that is specifically found on the trunk and extremities are distributed bilaterally and symmetrically. Buccal mucosa, tongue undersurface, and

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other mucous membranes may also get involved in pigmentation. Some over patterns like leucomelanosis, patchy pigmentation and diffuse hyper-pigmentation. Leucomelanosis has been found to occur in an arsenicosis patient who stops drinking arsenic contaminated water for some duration [25,26,27]. Keratosis due to arsenic involves palms and soles alone or in combination with nodules and distributed symmetrically. The nodular forms usually encounter on thenar, palms, fingers, heels and feet. Sometimes these small nodules may coalesce to form large lesions and in extreme cases fissures and cracks can also be formed in the soles. Keratosis can be further subdivided into mild, moderate, and severe. Mild form is nothing but an appearance of slight thickening or minute pales (< 2mm) in soles and palms, generally associated with grit like texture, may be detected by palpation. Moderate forms are numerous raised karatotic lesions (2-5mm) while as severe forms are very large discrete elevations (>5mm) on soles, palms, with horny look[24,27]. Histological examination of lesions reveals hyper keratosis, enlargement of rete ridges and acanthosis and in few cases, evidence of mitotic figure, and cellular atypiain big vacuolated epidermal cells [28]. First population based survey was conducted on 7863 individuals (4093females and 3590 males) in west Bengal in order to get a picture of keratosis prevalence in relation to arsenic exposure [26]. As per this survey report water arsenic content of individuals ranged from BDL (below detection limit) to 3.4mg/l however more than 80% of the individuals consumed water with arsenic level <0.5 mg/l. The age based prevalence of keratosis and pigmentation was significantly related to arsenic levels, increasing from zero to 0.3 in least exposure level (0.5mg/l) to 8.3 and 11.5 per 100 for females consumed contaminated arsenic water of >0.8mg/l respectively and rising from 0.2 and 0.4 per 100 in the lowest exposure group to 10.7 and 22.7 per 100 males in highest exposure of (>0.8mg/l) respectively. Men showed roughly 2 to 3 times more prevalence of both pigmentation and keratosis compared to women on consuming same arsenic dose in drinking water. 1.6-fold increase in the incidence of keratosis has been found in the individuals having 80% below standard body weight suggesting that malnutrition can also play role in increasing susceptibility. Results of a case study using more lifetime (at least 20 years) exposure assessment with less dose of (<0.5mg/l) in above population is also available [29]. The arsenic exposure assessment included arsenic contamination data from current and past water resources used in work places and households. The least arsenic consumption case was confirmed as 0.115 mg/l, significant dose response gradients with various concentrations were also observed [29]. In another case study of Bangladesh, a total of 1481 subjects aged more than 30 years exposed to arsenic concentration ranged from 0.01to 2.04 mg/l. This study revealed that 430 subjects out of total were found to have skin lesions due to arsenic and the overall prevalence was found as 29%. This study also confirmed that higher prevalence of arsenical skin lesions in males as compared to females with dose response relationship [30].

Respiratory Effects

Inhalation of high concentrations of arsenic compounds may irritate the respiratory system. Prolonged exposure of high concentration of airborne arsenic to smelter workers can have inflammatory effects and erosive lesions of the respiratory mucosa, including perforation of nasal septum. Lung cancer has been associated with chronic arsenic exposure in smelter workers and pesticide workers**.** First case of lung disease was reported from Antofagasta Chile [31]. In this study, 180 residents were exposed to arsenical drinking water of 0.8mg/l. About 38% of individuals showed abnormal skin pigmentation and chronic cough. Symptoms of chronic lung disease were found to be present in 57% of individuals caused by consuming arsenical drinking water in west Bengal [32]. Test of lung function was studied in 17 individuals and was revealed that 53% of patients have restrictive lung disease and 41% were found to possess combined restrictive and obstructive lung disease [31]. To correlate the chronic arsenic exposure relationship with lung disease occurrence, an epidemiological study was conducted in 6864 individuals of west Bengalin 2000 by Muzumder *et.al;* the participants included in this study have arsenical skin lesions and were highly exposed to water containing 0.5 mg/l of arsenic. Participants with low water arsenic concentration and normal skin were kept as control group. Prevalence odd ratio (POR) in participants having skin lesions were estimated for cough, shortness of breath and crepitations for males were 5,6.9, and 3.7 and for females 7.8, 9.6, 23.2 respectively [32]. Another study was conducted on 218 nonsmokers in Bangladesh, among these,94 were exposed to 0.136 to 1.0 mg/l of arsenic and remaining 124 were unexposed cases. The chronic bronchitis prevalence ratios were observed as 10.3 and 1.6 for females and males respectively [33]. In west Bengal, during 1998-2000, relationship between arsenical drinking water exposure and lung function was studied in 287 individuals from a population who were subjected to exposure of low dose arsenic exposure of upto 500µg/l [34]. Average forced expiratory volume in one second (FEV1) adjusted for smoking, height, and age was found to get reduced by 256.2 ml and the mean forced vital capacity (FVC) by 287.8 ml in men having skin lesions as compared to those having no skin lesions. Increasing 100µg/l arsenic in drinking water decreased FEV1 of 45ml and in FVC of 41.4 ml in men. Minimal evidence has been found for lung function alteration in case of women. Other than respiratory problems, reduced pulmonary function was also reported to be associated with the consumption of arsenical drinking water. In another study, 29 cases of chronic arsenic toxicity in a hospital survey for non-malignant lung diseases in Kolkata west Bengal[35]. In this study Interstitial lung disease was diagnosed in 31%, obstructive lung disease in 58.6% and bronchiectasis in 10% of participant cases. In order to ascertain the bronchiectasis incidence in the population, 108 individuals with arsenical skin lesions and 150 participants without skin lesions were studied in an arsenic rampant area of west Bengal[36]. Highest median arsenic concentration in drinking water was found to be 330µg/l in individuals with skin lesions as compared to

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28µg/l in those not having skin lesions. Among these, 38 of the individuals who complained for having at least two years of chronic cough went for high resolution computed tomography (HRCT), 27 participants with arsenical skin lesions were found to have 3.4 mean bronchiectasis severity score and 11 individuals without skin lesions were found to possess 0.9 mean bronchiectasis severity score (control). In participants who were reported for chronic cough, HRCT evidence of bronchiectasis was observed in 67% cases with skin lesions and in 27% controls[37]. Adjusted odds ratio of 10.1 was found as well. This investigation revealed that consuming high concentration arsenical water can increase bronchiectasis incidence in man. Several other studies also revealed chronic respiratory diseases like chronic cough or chronic bronchitis due to prolonged consumption of water contaminated with arsenic[38,39,40,41].

Gastro intestinal effects

The gastrointestinal effects of arsenic are commonly the result of ingestion; however, gastrointestinal effects may also occur after heavy exposure by other routes. Gastrointestinal effects are seen intensely after arsenic ingestion, and less often after inhalation or dermal absorption. The ultimate gastrointestinal lesion appears to be increased permeability of the small blood vessels, leading to fluid loss and hypotension. Widespread inflammation and necrosis of the mucosa and sub-mucosa of the stomach and intestine may occur and progress to perforation of the gut wall. A hemorrhagic gastroenteritis may develop, with bloody diarrhea as a presenting effect. In west Bengal, symptoms of dyspepsia has-been reported in 38.4% of the cases out of total 156 participants affected due to chronic arsenic toxicity cases[32]. However, no difference was found in abdomen pain incidence of the affected population exposed to arsenical drinking water against control population in an epidemiological investigation. (27.84 Vs. 31.81%)[42]. In the inner Mongolian region of china, a study was conducted for effect of arsenical drinking water on a test population which revealed that gastroenteritis affected 1447 cases of chronic arsenicosis due to arsenic concentration in water ranged from 0.05 to 1.8 mg/l[40]. Symptoms such as anorexia, diarrhea, nausea and abdominal pain were also reported by many investigators in chronic arsenic toxicity cases[23,33,43,44,45].

Hepatic Disorders

Acute arsenic toxicity may be associated with hepatic necrosis and elevated levels of liver enzymes. Arsenic intoxication may also result in toxic hepatitis with elevated liver enzyme levels. Earlier many investigators have reported the liver damage cases following treatment by arsenic as Fowler`s solution to patients [46,47,48] most of these patients were found to develop portal hypertension features with liver fibrosis signs. Typical cutaneous signs of long term exposure to arsenic were also found in few patients. Cases have also been reported for liver cirrhosis following medication with inorganic compounds of arsenic[49,50]. Portal hypertension linked with fibrosis has been also found in nine patients who possess high levels of arsenic in their level in Chandigarh (India). Two of these patients were found to consume drinking water containing arsenic concentration of 0.549 and 0.360 mg/l respectively[51]. Hepatomegaly was reported in 62 out of total 67 family members who consumed arsenical drinking water of concentration 0.2 to 2 mg/l in West Bengal while it was observed in only 6 out of 96 people who consumed safe and good water in the same area[23], thirteen out of those were having hepatomegaly due to arsenic were further studied in a hospital, fibrosis and portal zone expansion in liver histology were reported in almost all individuals but showed various degrees of severity. Evidence of enhanced intra-splenic pressure (30-36cm salne) in four patients out of five depicts portal hypertension. On splenopartography of these cases, intra hepatic portal view obstruction was reported, although liver functions were found to be normal and also bromsulphthale in retention test also normal results. Neutron activation analysis was used to estimate liver tissue arsenic level and was found in elevated amounts in 10 out of 13 cases (levels of Arsenic: cases-1.6±1.66mg/kg; Control-0.10±0.04mg/kg)[23]. In an another investigation, 190 individuals out of 248 were found to have hepatomegaly, 63 out of 69 hepatomegaly confirmed patients were biopsied showed evidence of portal fibrosis on the histology of liver. Serum globulin was observed to be high (>3.5g/dl) in 20.7% of the cases[52]. Another epidemiological investigation was conducted in west Bengal in which 4216 and 3467 individuals were exposed to arsenical drinking water above 0.05mg/l and below respectively, hepatomegaly incidence was found to have linear relation proportional to enhanced exposure in drinking water containing arsenic in both the sexes ($p_{<0.001}$)[42]. Several other investigators have also reported liver enlargement by consuming arsenic contaminated drinking water[25,39,40,41]. Almost all these investigations reported hepatomegaly, hepatic fibrosis and predominant lesions associated with prolonged consumption of arsenical drinking water.

Cardio vascular effects

Both acute and chronic exposure to high levels of arsenic may result in a varied range of adverse cardiovascular effects. There is limited strength of association between chronic arsenic exposure and peripheral vascular disease, hypertension, and cardiovascular disease. Acute arsenic poisoning may cause both diffuse capillary leakage and cardiomyopathy, resulting in shock. The extent of cardiovascular injury may vary with age, arsenic dose and individual susceptibility. In acute arsenic poisoning (such as suicide attempts), diffuse capillary leakage may lead to delayed cardiomyopathy, hypotension, shock, transudation of plasma and vasodilation.

In Taiwana form of peripheral vascular disease called as black foot disease has been found to be important complications of chronic arsenic toxicity. This is a unique disease characterized by peripheral arterial and severe systematic arteriosclerosis accompanied with dry gangrene and amputations at last stages. Black foot disease can be divided into two groups histologically, thromoboangitis

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Vol. 6 Issue 05, May - 2017

obliterans affecting small vessels in particular[53]. Actually black foot disease begins with patients complaining for numbness and coldness in feet which on progression over few years leads to ulceration, spontaneous amputation and gangrene. In a study of 40421 inhabitants in Taiwan, 8.9/1000 individuals were reported for black foot disease. Acrocyanosis and Raynaud's syndrome with various degrees of severity have also been reported in people consuming arsenical drinking water by several investigators[31,32,40,41,50,54]. The incidence of gangrene and amputation has-been found high in Taiwan while minimal in Chile, Bangladesh and India[55]. Enhanced black foot disease and a dose-response relation between inorganic arsenic exposure and hypertension prevalence had been reported by an epidemiological study[56]. In Chile a total of 382 men and 516 women were investigated from hyper endemic area of Taiwan which showed that 1.5 times increased hypertension prevalence compared to non-endemic areas, higher prevalence of hypertension was found to be associated with higher cumulative arsenic exposure[31]. The dose-response relationship has been found significant after adjusting for sex, proteinuria, body mass index, age, diabetes mellitus and serum triglyceride level. Enhanced hypertension prevalence was also observed in 6.2% of the individuals affected with skin lesions due to arsenic as compared to none without skin lesions in Chile[31].In Bangladesh, 1595 individuals were found to have enhanced hypertension risk associated with cumulative arsenic exposure[57]. A study of 263 participants affected with black foot disease and 2293 non-black foot disease participants was conducted in arsinocosis endemic area and was further followed up for five years, a monotonous biological gradient relationship has been observed ischemic heart mortality and cumulative arsenic exposure through consumption of artesian well water and relative risks were found to be 2.5,4.0 and 6.5 respectively for those having cumulative arsenic exposure of0.1 to 0.99, 10.0 to 19.9 and >20.0 mg/l compared to those without arsenic exposure after adjustment for age, sex, body mass index, cigarette smoking, serum cholesterol and try glyceride levels[27,55]. Moreover, increased incidence of cardio-vascular disease has been found related to ingested inorganic arsenic exposure especially ischemic heart disease has-been reported predominantly[58,59].

Disease of Nervous system

In studies that support n link, arsenic-exposed patients may develop destruction of axonal cylinders, leading to peripheral neuropathy. This has been testified at acute high doses (>2 milligram (mg) arsenic (As)/kilogram (kg)/day) as well as from repeated exposures to lower levels (.03 – 0.1 mg As/kg/day). Arsenic may cause encephalopathy at acute high doses (> 2mg As/Kg/day). Arsenic poisoning can cause peripheral neuropathy. The lesion is a sensory-motor axonopathy. The classic finding is a peripheral neuropathy involving sensory greater than motor neurons in a symmetrical, stocking glove distribution. In high-level arsenic exposures, onset of neuropathy may occur after 7 to 14 days, with strong increased sweating in the distal lower extremities, paresthesia, muscle tenderness, muscle cramps, numbness, and spontaneous pain Many investigators have reported the peripheral neuropathy incidence due to arsenical drinking water exposure[25,40, 41,44,60,61]. In west Bengal (India) 74 individuals (47.4%) have been found to have peripheral neuritis (limb weakness, tingling, numbness etc.) who were exposed to 0.5 to 14.2 mg/l of arsenical drinking water, 29 patients were subjected to objective evaluation of neuronal involvement depicted abnormal electromyography in 30 % and altered nerve conduction velocity in 38% of the patients[62]. Sensory neuropathy mostly electromyography has been observed in 10 out of 32 individuals exposed to arsenical drinking water concentration of 0.06 to 1.4 mg/l in Canada[63]. In an another electrophysiological investigation done on 88 individuals of arsenicosis in west Bengal, motor neuropathy was found in 27.3% and abnormal electromyography in 5.7% of the cases[64]. Many investigators have observed enhanced cerebro-vascular incidence in patients affected by chronic arsenicosis[40,59,60]. An investigation was done in order to study the relationship between cerebro-vascular disease prevalence and inorganic arsenic ingestion through drinking water exposure[65]. A sum of 8102 individuals were investigated in his study, cerebro-vascular disease status was recognized through personal interviews, home visits and by hospital record review as per WHO guidelines. Information such as cigarette smoking, consumption of alcohol habits, well- water consumption and socio- demographic features as well as disease history was collected. After adjustment for sex, hypertension, age, cigarette smoking, alcohol consumption and diabetes mellitus, a momentous dose-response relationship was found between cerebro-vascular disease prevalence and well-water arsenic concentrations. More significant biological gradient for cerebral infarction depicting multi-variate adjusted ratios of 6.9, 4.5, 3.4 and 1.0 respectively for those who were exposed to arsenical well-water concentration of >0.3, 0.051-0.299, 0.001-0.05 and zero mg/l. Sleep disturbances, weakness, peripheral neuritis, cognitive and memory impairment have been found in Byan College station residents Texas who were exposed to arsenic in air and water in the form of arsenic trioxide which was used for the production of defoliants in an Autochem plant[62]. Occurrence of headache has been found in several individuals who consumed arsenical drinking water in west Bengal[31] and Mexico[44].

Hematological Effects

Bone marrow depression may result from chronic or acute arsenic intoxication and may primarily manifest as pancytopenia. Both chronic and acute arsenic poisoning may affect the hematopoietic system. A rescindable bone marrow depression with pancytopenia may happen. Leukopenia and anemia are very common in chronic arsenic toxicity and are frequently accompanied by thrombocytopenia and mild eosinophilia. Chronic and acute poisoning has been found to be accompanied with hematological impairments[27]. Among 55 individuals who consumed arsenical drinking water in Japan for a period of five years, half of them had arsenical skin lesions and a characteristic decoration of thrombocytopenia, anemia and

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Vol. 6 Issue 05, May - 2017

leucopoenia[66]. Anemia was found in all the 13 individuals consumed arsenical ground water of 0.2 to 2 mg/l concentration in west Bengal. In another investigation on 156 individuals exposed to arsenical drinking water concentration of 0.05 to 14 mg/l presented occurrence of anemia in 47.4 % of the cases[31]. However, a simultaneous contrast with no prevalence of anemia was observed in the individuals exposed to well water concentration of 0.22 mg/l in Alaska[67] and in two towns of Utah where drinking water concentration of arsenic was 0.18 and 0.27 mg/l[68].

Diabetes

A dose-response relationship between incidence of diabetes and cumulative arsenic exposure has been observed in Taiwan on 891 persons residing in arsenic endemic area. The diabetes mellitus status was achieved by an oral glucose tolerance test and a regular diabetic history treated by insulin or sulphonylurea. A significant relation has been observed after adjustment for sex, age, body mass index and action level at work by a multiple logistic regression analysis providing a multivariate adjustment odds ratio of 10.05 and 6.61 respectively for those individuals who has an accumulative arsenic exposure of >15.0 and 0.1 to 15.0 mg/l compared with those who were not exposed. Due to the consumption of arsenical drinking water, significantly enhanced incidence of diabetes mellitus has been observed among the individuals having keratosis compared to those without such lesions in Bangladesh. An interested trend in risk between the incidence of diabetes mellitus and time weighed exposure strengthened the causal association possibility[69] however dearth of efficient and comprehensive long-term water sampling at water supplies in the targeted area is a constraint of the investigation because direct measurement of individual exposure data over time would have been desirable. However, these kinds of results reflected that diabetes mellitus may get induced by chronic arsenic toxicity.

Adverse pregnancy outcomes

Till now no certain evidence on pregnancy outcomes and infant mortality in relation with arsenical drinking water is accessible in literature but only a few examinations include assessment on individual intake of arsenical drinking water from all sources exposed during each pregnancy, still-births, post-neonatal and neonatal infant mortality has-been found to get amplified in raised arsenic exposure city of Antofagasta as compared to little exposure level city Valparaiso in Chile[70]. A boosted still-birth risk for women with present arsenic levels of >100µg/l has-been found in Bangladesh and additional inquiries have described an increased impulsive abortion effects as well[71]. However, no statistics was accessible on arsenic exposure during pregnancy and higher arsenic exposure levels 200µg/l or above were also not reflected separately in this investigation. In another earlier investigation from Bangladesh, rates of still births, spontaneous abortions and preterm delivery between 96 women residing in one village who were exposed to arsenical drinking water concentration >100µg/l to rates in 96 women from another village who were exposed to <20µg/l and reflected two to three folds more amounts among exposed women[72]. Both the above cited studies from Bangladesh described relation to exposure duration of women but have not taken into account the definite exposure time during pregnancy. A reflective investigation on infant death and pregnancy outcomes was conducted in west Bengal India, among 202 married ladies selected from a total population of 7683 between 2001 to 2003 years. Structural interviews were used to establish reproductive histories, 404 wells were examined and assessed as basis of water source to get the picture of arsenic exposure during each pregnancy. Generalized estimating equations based on logistic regressions were used to study Odds rates of still-births, impulsive abortions and infant mortality. Elevated concentrations of arsenic >200µg/l during pregnancy were found to be accompanied with six fold amplified still birth risk after adjusting for probable confounders. Enhanced still birth risk has been found in 12 women having arsenical skin lesions. However, no relation was found between impulsive abortion and arsenic consumption or infant mortality. This study confirmed that high concentration exposure of arsenic during pregnancy may increase still birth risk. However, no sign of enhanced rates of overall infant mortality and spontaneous abortion has been found[73].

Global Scenario and Indian perspective

Beyond permissible limits of arsenic level in drinking water is the chief cause of arsenic toxicity in the world. Taiwan, Chile, China, Mexico, Argentina, Hungary, India, Bangladesh, USA and Thailand have been reported for such type of contamination. More than 20 countries including India are in the midst of large scale threat caused due to chronic arsenic mass toxicity through arsenic contaminated ground water exposure; however, most people around the world affected due to arsenic toxicity in drinking water reside in Bangladesh, India and china[74]. Investigation by central ground water board of India revealed that arsenic contamination (>0.05mg/l) affects the states of west Bengal, Bihar, Assam, Chhattisgarh and utter Pradesh. The Bengal delta plain which includes Bangladesh and west Bengal in India is the most vulnerable area of ground water arsenic contamination, besides high level of arsenic has also been reported from Jharkhand and Manipur states of India. In west Bengal alone, 79 blocks in 8 districts have been reported for arsenic contamination in ground water beyond permissible limit of 0.05mg/l and about 162.6 lakh people (35.48% of total state population) reside in the risk zone[75]. In Bihar (India), the first report of arsenic contamination came from Bhojur district in 2002. Later on 57 blocks in 15 districts were identified as high arsenic contamination risk areas. Detailed investigations in Gangetic plain of Bihar revealed wide occurrence of arsenic along both the banks of river Ganga[76]. In addition to this three blocks of Sahebgunj, Rajmahal, Udohwa districts of Jharkhand have been reported for Arsenic contamination (0.05mg/l) because these areas are located on alluvial deposits[77]. An investigation carried out in Utter Pradesh of India revealed that 289 blocks of 49 districts are vulnerable to arsenic toxicity and it was found that 18

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districts have arsenic level of > 50ppb and 31 districts were found to have 10-50ppb in drinking water[78]. In India arsenic contaminations is primarily geogenic and mostly occur in consolidated sediments except in Chhattisgarh where its source has been found to occur in aquifers of Precambrian rocks.

Permissible limit

Earlier permissible limit of arsenic for drinking water was 50 ppb. Recently World Health Organization has abridged its permissible limit to 10ppb for drinking water purpose. In India, department of drinking water supply ministry of rural department has yet its 50ppb to be used for time being.

Treatment of Arsenicosis

Acute arsenic toxicity is almost not seen in the contemporary days, because there are many easier ways of suicidal and homicidal poisoning. Treatment is just like cholera and dehydration. The toxic properties of all arsenic preparations are dose-dependent. Regarding the administration of arsenic, the dictum of Paracelsus (1493 - 1541) is appropriate to remember: "Allsubstances are poisons; there is none which is not a poison. The right dose differentiates a poison and aremedy. "Arsenic is quickly cleared from the blood stream and the chief route of arsenic elimination is through the kidneys as methylated arsenic metabolites. Arsine exposure may also be evaluated by analyzing the content in hair and nails because arsenic tends to accumulate in these tissues over time. In cases of chronic arsenic poisoning one should consider BAL (British antilewisite) as a chelator[79]. During the clinical stage, when symptoms like melanosis and keratosis appear on the skin, chelating agents like BAL, Penicillamine help in dissipating melanosis. Mechanical scraping of soles of feet can be done to relieve keratosis. Urea and salicylate ointments can also be used[80]. In case of malignacy, clelating agents, become impractical. Early surgical removal of the affected parts (if no melanosis or granular spread) and chemotherapy may prolong life. But such treatments cannot antidote the disease after cancer sets in; they can only delay the suffering using highly lavish drugs. Dimercaprol (2,3-dimercaptopropanol) is the traditional chelating agent used, but Penicillamine has been used with some success. Parenteral dimercaprol is administered intramuscularly at an initial dose of 3 to 5 mg/kg of body weight every 4 hr. The dose should be tapered but under continuous administration until the urinary arsenic excretion is less than 50 kg per 24 hr. This therapy is often effective in preventing or neutralizing systemic toxicity. In most cases, the degree of recovery from neuropathy, aplastic anaemia, encephalopathy and jaundice is limited and directly related to the initial severity of the systemic involvement and the rapidity with which chelation therapy in initiated. A recently reintroduced drug that seems to be a promising agent for treating arsenic poisoning is 2, 3-dimer captosuccinic acid. This is a dithiol agent that can be orally administered and has few reported side effect[81].

PREVENTION OF ARSENIC POISONING IN HUMANS

It is clear that high-arsenic drinking water may be a factor in arsenic toxicosis in human beings. It appears to be important in the control of the disease to consider how to prevent arsenic intake from drinking water. The symptoms and signs of arsenic poisoning may lessen if the quality of drinking water is improved. In some cases, the symptoms and signs of arsenic poisoning were reduced three years after the quality of drinking water enhanced. The morbidity rate also dropped. Numerous studies suggested that upgrading of water quality, the rate of improvement in the symptoms and signs of arsenic poisoning in human beings may increase with a decrease in arsenic level in the drinking water source. Furthermore, it was detected that new cases of human poisoning occurred only when arsenic concentrations in the drinking water source exceeded 0.15 mg/L. At the same time, it was also found that arsenic levels in the urinary samples from cases of human poisoning also declined with a decrease in the arsenic levels in water source for drinking. Thus, it may be vital for the control of the disease to improve water quality in areas of endemic arsenic toxicosis[82].

Management of chronic arsenic toxicity

Chronic arsenicosis leads to permanent damage in several vital organs, and arsenic is a recognized carcinogen. Though there is no substantial morbidity of milder form of the disease, mortality is high in severe cases. Despite the degree of this potentially fatal toxicity, there is no actual therapy for this disease. Complications of moderate and severe form of arsenicosis may not be barred even after remediation of the arsenic-contaminated water. However, people should be instructed to stop drinking arsenic contaminated water or exposure to arsenic from many other sources. To determine the consequence of providing safe water to affected people, a cohort of 24 patients with chronic arsenicosis were re-examined after consumingarsenic-free water (<10 µg/l) for a period varying from 2to 10 yr (13 patients 10 yr, 11 patients 2-5 yr) in West Bengal. These people had been drinking arsenic contaminated water (0.13-2.0 mg/l) for 4-15 yr. Partial perfection of pigmentation and keratosis were observed in 45 and 46 per cent of patients, respectively. However, liver enlargement was insistent in 86 percent of cases. The most worrying observation was the new appearance of signs of chronic lung disease (shortness of breath, cough and chest signs) in 41.6 per cent of cases. There was a minor reduction of clinical signs of neuropathy[83]. Study reports are available on variationsof severity of skin lesions amongst an affected cohort of arsenicosis patients in Southern Thailand where interferences to reduce arsenic contaminated water had-been executed. Over 10-year period, both regression and progression of lesions occurred, though the majority of the subjects followed up remained the same. Drinking principally arsenic free water increased the probability of regression in subjects with mild stage lesions but not in those with more radical stage lesions. By contrast, high arsenic content in the household wellwater, even though it

International Journal of Engineering Research & Technology (IJERT)
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Vol. 6 Issue 05, May - 2017

was not used for drinking, reduced the probability of lesion regression among the subjects in more advanced stage but not among milder stage cases. Regardless of initial stage a period of absence from the affected area increased the likelihood of lesion regression[84]. Another cohort follows 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 drinking safe water during the previous 5 years, the skin lesions cleared or decreased in 49.7 percent of people. However, out of 306 people who did not have such lesions previously, new skin lesions appeared in 32(10.5%)[85]. Skin lesions were conveyed 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 substantial improvement of skin lesions, while the potential risk of arsenic induced cancers after cutting offhigh arsenic exposure was still ambiguous and indefinite[86].

From the results of these studies it is clear 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 inspite of stoppage of consumption of arsenic contaminated water. Further, there rests 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 supposed to be the specific therapy for relief of systemic clinical manifestations and reduction of arsenic stocks in the body, dropping 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 generated better efficacy than control subjects treated with place[87].But in another study, chelating agent DMPS (dimercaptopropane sulphonate) demonstrated significant upgrading of clinical score among drug treated cases compared to controls in a single blind placebo control trial. Augmented urinary excretion of arsenic during the period of drug therapy was also confirmed during the study [88]. However, the drug is costly, not available locally and reports of long-term clinical trial are notavailable. Therefore, the drug could not be suggested currently for routine use for chronic arsenocosis patients in India. Development of symptoms of arsenicosis patients in Bangladesh have been reported to occur following use of antioxidants like vitamin A, C and E[89]. However, no placebo controlled trial with the vitamins has been carried out nor the toxicity of their long-term use has been established. Supportive treatment could help in dipping many symptoms of these patients. Treatment in hospital with good nutritious diet has been found to shrink symptom score in subsets of placebo treated arsenicosis patients during the course of DMSA and DMPS trial[89,90]. Currently the most prevailing practice of symptomic treatment of keratosis is to apply locally 5-10 percent of salicylic acid and 10-20 percent urea based ointment onkeratotic skin lesions[24]. Higher doses need further evaluation. Though specific treatment for chronic arsenic toxicity has not yet been fully recognized, supportive and symptomatic treatment could help in decreasing many symptoms of the patients. Arsenic tempted cancers could be cured if noticed early. Hence a good cancer surveillance programme in chronic arsenic exposed population is vital 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 drinking if found contaminated. In summary, principal manifestation of chronic arsenic toxicity are skin lesions characterized by pigmentation and keratosis. However, it produces protean systemic manifestation over and above skin lesions, significant ones being chronic lung disease like chronicbronchitis, liver disease like non cirrhotic portalfibrosis and other diseases like polyneuropathy, chronic obstructive pulmonary disease and bronchiectasis, peripheral vascular disease, diabetes mellitus, non-pitting edema of feet/hands, hypertension and ischeamic heart disease, weakness and anemia. Cancer of skin, lung and urinary bladder are main cancers linked with chronic arsenic poisonousness.

Technologies available for removal of arsenic from drinking water

Following are the different techniques available for removal of Arsenic from drinking water.

1. Reverse Osmosis and electro dialysis
2. Bioremediation and *In-situ* remediation
3. Coagulation-Flocculation-Sedimentation-filtration (Co-precipitation)
4. Oxidation of Arsenic (III)
5. Iron coated sand
6. Low pressure Nano filtration
7. Ion exchange
8. Passive sedimentation
9. Adsorption on different media
10. Solar oxidation

For mitigation of arsenic in water to step up some necessary steps:

Surface water based piped water supply system wherever feasible, is the most suitable and sustainable solution for arsenic difficulties in groundwater based drinking water sources.

- Provide Spot test facility and recorded affected location.
- One call center in every District to Registered affected Person. There must also be an isolated Department constituted in the District hospital for treating arsenicosis.
- Medical person employ by state Govt. with arsenic mobile team, which find out number of patient in specific area like in a block -wise, in a village-wise. .
- Mass consciousness programs.

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Vol. 6 Issue 05, May - 2017

FUTURE RESEARCH SCOPE

The environmental condition of exposures to Arsenics has generated the chief avenues of contemporary research. So far, only scarce environmental studies include a speciation of Arsenic (e.g., inorganic trivalent/pentavalent forms), and the existing results are not totally uniform[91,92]. Therefore, it ought to be projected that Arsenic speciation exploration will further develop. Associated with this field, a principal research point of the last years has been adsorption, distribution, metabolism and excretion (ADME) of Arsenic species/compounds[93,94]. It was soon documented that toxicities of Arsenic (III) and Arsenic (V) are unlike[95] and that the toxicity of As (V) results in part from its reduction to As (III)[96]. Metabolism of inorganic Arsenic proceeds largely by a sequence of repetitive reduction and oxidative methylation steps, the latter mediated by arsenic methyl transferase (CYT19)[97]. It has been demonstrated that arsenic-glutathione complexes are substrates for the human CYT19. In general, toxico-kinetics of Arsenic species remained a significant experimental research focus[98].

In addition to this there may be relevant environmental co-exposures of Arsenic with other inorganic compounds that lead to mutual action, with questions of the mechanisms involved. For instance, Lin *et.al* addresses apoptotic mechanisms induced by co-exposure with barium, which can additionally be present in Arsenic-containing drinking-water wells. Other publications report co-exposures of arsenic and fluoride[99]. Thus, Ma *et.al* describes a population- based study in a rural area in Northwest China with a large number of cases diseased with a blend of fluorosis and arseniasis. The causal factor was again indoor burning of coal rich in both Arsenic and F, which led to enormously high co-exposures through the inhalation route[100]. In an experimental study on rabbit aorta as a cardiovascular showed that inflammatory responses play a serious role in the combined cardiovascular toxicity of Arsenic and F[101]. Indeed, with respect to the different expressions of toxicity of arsenic[102], cardiovascular disorders, such as hypertension, atherosclerosis and myocardial injury, are receiving augmented interest[103]. A mechanism likely to be tangled is oxidative stress[104].The entire field of As-induced oxidative stress and related signaling pathway is evidently of increasing scientific relevance[105]. Mechanisms of Arsenic-induced carcinogenesis are a significant area of research[106]. Authors from top governmental U.S. organizations (NTP, NIEHS, NCI) raised serious concern of trans-placental carcinogenesis by a specific Arsenic compound, methyl arsenous acid[107]. Against such a background, the priority of current research into mechanisms of Arsenic-induced malignant transformation is evident. There is an extraordinary development of genetic polymorphism studies, in conjunction with epidemiological research in Arsenic exposed populations. A study suggests a specific role of the glutathione S-transferase GST01-1 in Arsenic-mediated inflammatory response and apoptotic processes, and the idea is being put forward that A140D and E208K polymorphisms rise the risk for inflammatory and apoptosis-related diseases in Arsenic exposed populations. The role of GST01 polymorphisms as a modifying factor of Arsenic toxicity has been established in another study[108]. Gene-environmental interactions focusing on human Arsenic exposures and Arsenic-induced effects are a very striking and rapidly developing research area.

CONCLUSION

Arsenic contamination of groundwater and associated health hazards are becoming High-profile problems throughout the world. Number of Aquifers has been identified with problems of high Arsenic concentration in ground water. Safe water is not a claim of single person; it's the problem of mainstream population. The instant symptoms of acute arsenic poisoning comprise abdominal pain, vomiting and diarrhea. These are tracked by impassiveness and tingling of the extremities, muscle cramping and death, in extreme cases. The first signs of long-term exposure to high levels of inorganic arsenic (e.g. through drinking-water and food) are typically indicated in the skin, and include skin-color changes, skin scratches and hard patches on the palms and soles of the feet (hyperkeratosis). These occur after a least exposure of about five years and may be a pioneer to skin cancer. In addition to skin cancer, longstanding exposure to arsenic may also cause cancers of the bladder and lungs. The International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as carcinogenic to humans, and has also stated that arsenic in drinking-water is oncogenic to humans. Other hostile health effects that may be allied with long-term ingestion of inorganic arsenic include growing effects, diabetes, neurotoxicity and cardiovascular disease. As mentioned above, in China (Province of Taiwan), arsenic exposure has been related to "blackfoot disease", which is a severe disease of blood vessels leading to infection. However, this disease has not been found in other parts of the world, and it is imaginable that underfeeding contributes to its development. Most of the people suffering from arsenicosis, they belong to very poor family and their socio-economic status is very low, so they not able to use costly technique for mitigation of arsenic in water. Various Arsenic mitigation choices include using surface sources, discovering and harnessing alternate arsenic free aquifer, elimination of Arsenic from ground water using treatment filters and rainwater harvesting are used but proper execution is essential task. We must realize that so far there is no available medicine for chronic arsenic toxicity; safe water, nutritious food, vitamins and physical exercise are the only precautionary measures to fight the chronic arsenic toxicity.

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