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Chronic Arsenic Intoxication in Asia: Current Perspectives

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Chronic Arsenic Intoxication in Asia: Current Perspectives

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Abstract

Chronic arsenic intoxication has been an issue of public health concern in some countries in Asia, such as Taiwan, Mainland China, Bangladesh, India, and Thailand. In Taiwan, an endemic peripheral vascular disease known as 'blackfoot disease' (BFD) located in a confined area along the southwestern coast of Taiwan attracted the attention of the government and the scientific professionals since mid-twentieth century. The arsenic contents of the drinking water taken from the artesian well were found to be higher than the normal standard value. Epidemiologic studies confirmed the association between arsenic exposure and BFD. Besides, the residents of this area were also found to have higher prevalence rates of skin lesions (hypo/hyperpigmentation, hyperkeratosis, and skin cancers), bladder cancer, ischemic heart disease, hypertension and diabetes mellitus etc. than other areas of Taiwan. In China, arsenic-related diseases have been noted since 1980s. Three routes of arsenic intoxication can be identified there. In Inner Mongolia and Xinjiang province, the source of exposure is from drinking water; while in Guizhou and Yunan provinces, the sources of exposure are from coal burning and air pollution, respectively. Typical arsenical skin lesions can be observed in the exposed people in China. In Bangladesh and West Bengal-India, the major exposure source is groundwater pumped up from tube-wells. These two areas have the most serious problem of groundwater contamination with arsenic in the world today. Millions of people are exposed to drinking water with arsenic concentrations beyond safety levels in these two countries. The problem has only been recently attended by the international societies, which are now working together to solve the problem. In a localized area of Thailand, surface drinking water is contaminated with arsenic from the process of mining. The general belief and practice of the villagers in this area hampers the replacement of the drinking water with rainwater. (J Intern Med Taiwan 1999;10:224-229)

Key Words：Arsenic, Chronic intoxication, Endemic disease, Water pollution, Air pollution, Coal burning, Asia

Introduction

Arsenic is a ubiquitous element in nature. It can be found in soil, air, water, food, or some medications. Inorganic forms of arsenic are much more toxic than organic forms. Acute intoxication can cause a variety of symptoms and signs involving the gastrointestinal, dermal, nervous, renal, hepatic, hematopoietic, cardiovascular, respiratory and oph-

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thalmic systems[1,2]. Long-term exposure to arsenic can cause atherosclerosis and cancer[1,2]. Chronic intoxication can be resulted from long-term exposure to sublethal dosage of arsenic from drinking water, coal burning or industrial sources. Because of the requirement of long gestation time for visible effects to occur, chronic intoxication can cause the occurrence of a variety of endemic diseases once the duration and dosage of exposure to arsenic in a localized population reaches its threshold. Arsenic-related endemic diseases have been discovered over the past decades. In Asia, the issue of chronic arsenic intoxication seems to be an important public health problem in some countries and areas. The most important source of contamination is the drinking water. The World Health Organization (WHO) established 0.2 mg/L as an allowable concentration in the first version of International Standards for Drinking-Water in 1958[3]. In the second version published in 1963, a stricter concentration of 0.05 mg/L was set as a new standard[3]. A further stricter standard of 0.01 mg/L was suggested as a provisional guideline in the last edition of the WHO Guidelines for Drinking-Water Quality published in 1993[3]. In this paper, the current status of chronic arsenic intoxication causing endemic diseases of public health concern in Asia is reviewed.

Taiwan

During the second half of the 20th century, an endemic peripheral vascular disease known as 'blackfoot disease' (BFD) in a confined area along the southwestern coast of Taiwan attracted the research interest of local and foreign scientists. The first case report of this disease can be traced to early 1900s[1]. This disease was characterized by numbness and coldness of one or more extremities, which might progress to intermittent claudication, gangrene, and spontaneous amputation[1]. The prevalence of BFD in endemic area in Taiwan averaged 2.1 per 1,000 and was as high as 17.9 per 1,000 in hyperendemic villages[4]. At the same time, the prevalences of skin lesions such as hyperpigmentation, hyperkeratosis and skin cancers were also noted to be higher in the residents of this area[5]. The coexistence of skin lesions and BFD was high in the villagers[5]. Epidemiologic studies in 1960s showed a strong relationship between high concentrations of arsenic in drinking water taken from the artesian wells and skin cancer, keratosis and blackfoot disease[5,6]. The etiology of these endemic diseases had been suspected to be associated with the consumption of artesian well water, which was dug out from the earth as deep as 100-300 meters[1]. High concentrations of arsenic were found in the well water[7,8]. The arsenic contents of artesian well water in the BFD area have been reported to range from 0.35 to 1.14 mg/L with a median of 0.78 mg/L[7], whereas the median arsenic content of well water in the nearby nonendemic area was 0.01 mg/L[8]. The source material of the arsenic in the BFD area is not as yet known, but is likely to be pyrite material or black shale occurring in underlying geological strata[9]. On exposure to air, oxidation of the pyritiferous material would lead to the release of sulfuric acid and the solubilization of arsenic[9].

Because of the link of the etiology of these endemic diseases with the artesian well water, the Provincial Government of Taiwan began to implement tap water supply system to this area and even programs of moving villagers to other residential areas had been carried out. The incidence rates of blackfoot disease and skin lesions decreased dramatically after the implementation of tap water supply system to the endemic villages during 1970s. Nowadays, sporadic cases of BFD can still be found. However, most of them are over 50 years of age.

Further investigation established the relationships between high arsenic exposure and cancers of the bladder and other internal organs[10]. More recent studies also established the association between arsenic exposure and ischemic heart disease[11], peripheral vascular disease[12,13], stroke[14], hypertension[15], diabetes mellitus[16,17], and microcirculatory defects[18].

China

In early 1980s, chronic arsenic intoxication from drinking deep well water with arsenic levels over 0.6 mg/L was first recognized in Xinjiang province of Mainland China[19]. A decade later, similar arsenic poisoning was found in Inner Mongolia and Shanxi province[19]. Other sources of arsenic poisoning from burning high arsenic-containing coal in Guizhou province and from air pollution from non-ferrous smelters in Yunan province were found later[19].

Inner Mongolia is an autonomous region located on the northern part of China. Its capital is Huhhot. In the western part of Huhhot, high concentrations of arsenic are found in the drinking water obtained from underground. The arsenic in the underground water is mainly released from the local rock, and not from arsenical pesticides[20]. The residents of this area are not exposed to arsenic from other sources such as factories, mines or other industries. Examination of the surface soils, air, fish and crops etc. did not reveal arsenic levels above standards[20]. In a survey of 355 water samples obtained from 17 surface water samples and 33 and 305 deep and shallow wells, the arsenic concentrations above 0.05 mg/L were 0%, 54.6% and 20.7%, respectively[20]. Determination of the arsenic valence in these water samples revealed a predominance of As^{+3} of 52-75% in the shallow and deep wells[20]. In May 1990, cases of chronic arsenicism with characteristic dermatologic manifestations such as hypo/hyperpigmentation and hyperkeratosis, and in severe cases, squamous cell carcinoma, basal cell carcinoma, and Bowen's disease, were first recognized at Zhi Ji Liang village in the Huhhot area[20]. Later studies also confirmed the findings. In a later epidemiologic survey of 3 villages, namely the Tie Men Geng, Zhi Ji Liang and Black River (Hei He), 3,185 out of 3,329 (95.7%) residents were clinically examined. For those consuming water with arsenic concentrations below 0.05 mg/L, none of them had manifestations of chronic arsenicism. However, for those who consumed water containing arsenic levels above 0.05 mg/L, dermatologic manifestations of chronic arsenicism were found in 20.1% of the residents. A dose-response relationship between dermatologic manifestations of chronic arsenicism and arsenic concentrations in drinking water was observed in residents consuming water containing arsenic above 0.05 mg/L[20]. However, no cases similar to blackfoot disease as observed in Taiwan were observed in the Inner Mongolian studies[20].

In Guizhou Province, which located on the southwestern part of China, high arsenic containing coal is used for heating, cooking, and drying foods such as chilli peppers and corn. The arsenic content of coal in this area ranges from 85.0 to 8300 mg/kg, with an average of 876 mg/kg[21]. High arsenic levels are found in kitchen dust, indoor air, and foods. Corn and chilli peppers dried indoors over coal-burning stoves have arsenic contents of 5-20 mg/kg (ppm) and 100-800 mg/kg, respectively[22]. The arsenic concentration of the air is as high as 0.04-0.13 mg/m^3, 10-40 times higher than the standard[19]. However, drinking water does not appear to be an important source of arsenic exposure, because the arsenic content in drinking water is below 0.05 mg/L[22]. The sources of arsenic exposure in the endemic area of Guizhou were estimated to be 50-80% from food, 10-20% from air, 1-5% from water, and 1-3% from indoor flying ash[22]. People living in this area were estimated to have arsenic intake amounting to 6.67 mg in spring, summer, and autumn, and 7.88 mg in winter, respectively[21]. Typical arsenic-related skin lesions such as hypo/hyperpigmentation, hyperkeratosis, Bowen's disease, and squamous cell carcinoma etc. have been observed in the exposed residents.

In Yunan province, a different route of arsenic exposure was found. In a township with a population of over 100,000, air polluted with arsenic emitted from non-ferrous smelter exceeding several folds of maximum allowance was noted[19]. The polluted air contaminated the crop (such as rice and corn) grown in that area. It was estimated that the main source of arsenic exposure of the residents was 90% from the intake of the food and 10% from the inhalation of the air[19]. The daily intake of arsenic was estimated as 0.3-1.1 mg[19]. The daily intake of inorganic arsenic has been suggested by the World Health Organization not to exceed 2μg per kg body weight[23].

Bangladesh and West Bengal-India

Bangladesh and West Bengal-India have the most serious problem of groundwater contamination with arsenic in the world today. The total area of Bangladesh is 148,393 km^2 and the population is 120 millions. The total area and population of West Bengal-India are 89,192.4 km^2 and 60 millions, respectively. In a massive survey of 12,084 and 55,166 tubewells from 64 districts of Bangladesh and 9 affected districts of West Bengal-India, respectively, arsenic concentrations above 0.05 mg/L were found in more than one third of the samples[24,25]. About 95% of the 120 millions people in Bangladesh drink tubewell water. Tracing back in history of Bangladesh, surface water was replaced by tubewell water in recent 30 years, because diarrheal diseases associated with drinking surface water caused the majority of morbidity and mortality in children in Bangladesh[26]. Analyses revealed that 81%, 94%, and 95% of the samples obtained from hair, nail, and urine, respectively, in residents of Bangladesh, and 57%, 83%, and 92% of the respective samples obtained from residents of West Bengal-India had arsenic levels above normal[24]. Arsenical skin lesions can be found in 24.5% and 15.0% of the people living in Bangladesh and West Bengal-India, respectively[24]. Cases of gangrene and skin cancer can also be found in these affected areas[24,25]. According to a community-based survey of diabetes mellitus in Bangladesh, a dose-response trend was also observed between the prevalence of diabetes mellitus and arsenic level in water [27]. This finding is in conformation to our studies carried out in blackfoot disease-hyperendemic villages in Taiwan[16,17]. However, because of the lack of standardized studies, the accurate prevalence rates of the diseases and their relationship with arsenic exposure require further clarification.

Thailand

In 1987, the skin cancer of a female living in Ronpibool district of Nakhon Sri Thammarat Province located at southern Thailand led to the discovery of an endemic area with chronic arsenic poisoning[28]. The sources of the arsenic are high-grade arsenopyrite waste piles and alluvial mineral deposits[9]. Alluvial soils contained up to 5,000 mg/g arsenic[9]. Most of the arsenic existed in the waste materials as insoluble scorodite ($FeAsO_4 2H_2O$) with only small amount of the primary arsenopyrite[9]. The source of arsenic poisoning was believed to be the surface water. Shallow well water could also be contaminated with arsenic up to 5 mg/L[9]. However, well water from deeper than 60 feet from the level of limestone and slate is safe[28]. A geological investigation postulated that the contamination of surface drinking water was from arsenopyrite (FeAs), probably related to the mining process that had taken place for a hundred years[28]. Villages of higher prevalence rates also demonstrated higher percentages of arsenic contamination of over 0.05 mg/L[28]. Soil and food grown in villages of high prevalences of chronic arsenic poisoning also contained higher levels of arsenic (22-250 mg/kg)[29]. Although the government of Thailand provided thousands of big water jars for the villagers as rainwater container, traditional belief and practice prohibits them from using rainwater. It is the general belief of the villagers that pregnant women would contract a severe illness called 'Sannibat Nar Fai' and die if they touch rainwater and that women getting into the big water jars to wash them would cause bad luck for their families[28]. Besides the clinical manifestation of arsenic skin lesions, children's intelligence was also found to be inversely related to the arsenic levels in the hair of the children after adjusting for confounders[30]. Arsenic was found to explain 14% of the variance in children's intelligence in this area [30]

Conclusions

The status of chronic arsenic intoxication in these endemic areas in Asia is summarized in Table 1. Although BFD is perishing in Taiwan after the implementation of tap water in the endemic area, the conditions in other emerging endemic areas are critical. Remedial measures should be taken by the local governments and the scientific professionals. New sources of water and coal with low arsenic contents, techniques for arsenic removal from drinking water, decreasing industrial arsenic emissions and promoting health education among the involved people are necessary. Up to now, there is no 'magic bullet' for the treatment of the diseases associated with arsenic intoxication. The best strategy is prevention and avoidance of exposure.

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References

1. Tseng CH. Peripheral vascular disease and microcirculatory defects among residents in the endemic areas of blackfoot disease. Ph.D. Dissertation of Graduate Institute of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan, 1996.
2. Chen CJ, Chiou HY, Huang WI, et al. Systemic non-carcinogenic effects and developmental toxicity of inorganic arsenic. In: Abernathy CO, Calderon RL, Chappell WR eds. Arsenic: Exposure and Health Effects. Chapman & Hall Press, 1992:124-34.
3. Yamamura S. Arsenic and fluoride in drinking water; WHO's recent endeavours. World Health Organization, Geneva, Switzerland for the Pan-Asia-Pacific Conference on Fluoride and Arsenic Research, August 16-20, 1999, Shenyang, China.
4. Wu HY, Chen KP, Tseng WP, Hsu CL. Epidemiologic studies on blackfoot disease. I. Prevalence and incidence of the disease by age, sex, year, occupation and geographical distribution. Memoirs College Med Natl Taiwan Univ 1961;7:33-50.
5. Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenism in Taiwan. J Natl Cancer Inst 1968;40:453-63.
6. Tseng WP. Effects of dose-response relationships on skin cancer and blackfoot disease with arsenic. Environ Health Perspect 1977;19:109-19.
7. Chen KP, Wu HY, Wu TC. Epidemiologic studies on blackfoot disease in Taiwan 3. Physicochemical characteristics of drinking water in endemic balckfoot disease areas. Memoirs College Med Natl Taiwan Univ 1962;8:115-29.

Table 1. Chronic arsenic intoxication in Asia

Area	Sources of exposure	Reported clinical associations	
		Skin lesions	Others
Taiwan	Deep well water	+	Blackfoot disease, cancers, hypertension, diabetes mellitus
China			
Guizhou	Coal-burning	+	
Inner Mongolia	Shallow and deep well water	+	
Bangladesh and West Bengal-India	Tube well water	+	Diabetes mellitus, gangrene
Thailand	Surface and shallow well water	+	Childrens' intelligence

8.Lo MC, Hsen YC, Lin BK. The second report on the investigation of arsenic content in underground water in Taiwan Province. In: Provincial Institute of Environmental Sanitation, Taichung, Taiwan, 1977:1-21.

9.Thornton I, Farago M. The geochemistry of arsenic. In: Abernathy CO, Calderon RL, Chappell WR, eds. Arsenic: Exposure and Health Effects. Chapman & Hall, 1992:1-16.

10.Chen CJ, Chen CW, Wu MM, Kuo TL. Cancer potential in liver, lung, bladder and kidney due to ingested inorganic arsenic in drinking water. British J Cancer 1992;66:888-92.

11.Lin LJ, Horng SF, Liaw KF, et al. Arsenic and ischemic heart disease in the blackfoot disease-endemic area (in Chinese with English abstract). Chin J Public Health (Taipei) 1995;14:502-11.

12.Tseng CH, Chong CK, Chen CJ, Tai TY. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. Atherosclerosis 1996;120:125-33.

13.Tseng CH, Chong CK, Chen CJ, Tai TY. Lipid profile and peripheral vascular disease in arseniasis-hyperendemic villages in Taiwan. Angiology 1997;48:321-35.

14.Chiou HY, Huang WI, Su CL, Chang SF, Hsu YH, Chen CJ. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 1997;28:1717-23.

15.Chen CJ, Hsueh YM, Lai MS, et al. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 1995;25:53-60.

16.Lai MS, Hsueh YM, Chen CJ, et al. Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 1994;139:484-92.

17.Tseng CH, Tai TY, Chong CK, et al. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis hyperendemic villages in Taiwan. In: Pan-Asia Pacific conference on fluoride and arsenic research: program and abstract book. Shenyang, China, 1999:23.

18.Tseng CH, Tai TY, Lin BJ, Chen CJ. Abnormal peripheral microcirculation in seemingly normal subjects living in blackfoot disease-hyperendemic villages in Taiwan. Int J Microcirc 1995;15: 21-7.

19.Niu S, Cao S, Shen E. The status of arsenic poisoning in China. In: Abernathy CO, Calderon RL, Chappell WR, eds. Arsenic: Exposure and Health Effects. Chapman & Hall, 1992:78-83.

20.Luo ZD, Zhang YM, Ma L, et al. Chronic arsenicism and cancer in Inner Mongolia: Consequences of well-water arsenic levels greater than 50 $\mu g/l$. In: Abernathy CO, Calderon RL, Chappell WR, eds. Arsenic: Exposure and Health Effects. Chapman & Hall, 1992:55-68.

21.Zheng B, Ding Z, Huang R, et al. Issue of health and disease relating to coal use in southwestern China. Int J Coal Geology 1999;40:119-32.

22.Zheng BS, Ding ZH, Zhu JM, Zhang J, Long JP, Zhou DX. The major ingestion pathways of arsenic in endemic arsenosis areas in Guizhou Province, China. In: Pan-Asia Pacific conference on fluoride and arsenic research: program and abstract book. Shenyang, China, 1999:44.

23.WHO (World Health Organization). Chapter 2: Chemical aspects. In: WHO Guidelines for Drinking Water Quality. Vol. 2: Health criteria and other supporting information. WHO Draft Geneva, Switzerland 1992:151-8.

24.Chowdhury UK, Biswas BK, Chowdhury R, et al. Arsenic groundwater contamination and sufferings of people in Bangladesh and West Bengal-India. In: Pan-Asia Pacific conference on fluoride and arsenic research: program and abstract book. Shenyang, China, 1999:27.

25.Chowdhury TR, Mandal BK, Samanta G, et al. Arsenic in groundwater in six districts of West Bengal, India: The biggest arsenic calamity in the world: The status report up to August, 1995. In: Abernathy CO, Calderon RL, Chappell WR, eds. Arsenic: Exposure and Health Effects. Chapman & Hall, 1992:93-111.

26.Hoque BA, Yamamura S, Heijnen HA, Morshed G, Khan F. Arsenic problem in drinking water in Bangladesh context. In: Pan-Asia Pacific conference on fluoride and arsenic research: program and abstract book. Shenyang, China, 1999:21.

27.Rahman M, Tondel M, Ahmad SA, Axelson O. Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 1998;148:198-203.

28.Choprapawon C, Rodcline A. Chronic arsenic poisoning in Ronpibool Nakhon Sri Thammarat, the Southern Province of Thailand. In: Abernathy CO, Calderon RL, Chappell WR, eds. Arsenic: Exposure and Health Effects. Chapman & Hall, 1992:69-77.

29.Division of Environmental Health, Department of Health. Report on summary of intervention for chronic arsenic poisoning in Ronpibool District, Nakhon Sri Thammarat Province, 1989.

30.Siripitayakunkit U, Visudhiphan P, Pradipasen M, Vorapongsathron T. Assocication between chronic arsenic exposure and children's intelligence in Thailand. In: Pan-Asia Pacific conference on fluoride and arsenic research: program and abstract book. Shenyang, China, 1999:22.