

SYNDROME OF ENDEMIC ARSENISM AND FLUOROSIS

A CLINICAL STUDY

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Sixty-five patients in Xinjiang with syndrome of endemic arsenism and fluorosis (SEAF) were investigated clinically from March 1982 to August 1989. SEAF is a kind of chronic syndrome resulting from the combined, harmful effects of two trace elements, arsenic and fluorine. Peripheral neuritis and cardiovascular changes were observed in this syndrome more often than in simple arsenism or simple fluorosis. The excessive quantities of these two trace elements in blood might have a synergic, harmful effect on the nervous and circulatory systems. No definite conclusion could be reached with regard to the morbidity of skin and visceral tumors in this series. The incidence of associated skin cancer was found to be 7.7% and an associated Grade II squamous cell carcinoma of the esophagus was encountered in one patient.

There is an artesian well in Kuitun Area, Xinjiang. The arsenic content in the well water is 0.6 mg/L, 12 times the normal permission in drinking water (0.05 mg/L in this country) and fluorine content is 3.45 mg/L, 3.45 times the normal permission (1mg/L). The local residents have begun drinking the well water since October 1969. Since then more and more patients manifesting both arsenism and fluorosis had been found. In 1985, Qian et al¹ reported 56 cases of endemic arsenism complicated by intoxication with fluorine. As it is essentially a combined intoxication caused by the two trace elements, arsenic and fluorine, it would be appropriate to change the term to the syndrome of endemic

arsenism and fluorosis (SEAF). This paper is a clinical study of 65 cases of SEAF found from March 1982 to August 1989.

PATIENTS AND METHODS

All the 65 patients were permanent residents who drank the well water in that area. The survey began in March 1982, and the patients were examined in 1984 (prior to the water reform) and again in 1989 (five years after the reform). They were subject to general physical examinations and radiography of the pelvis and extremities. In some patients, ECG, EMG, fiberoptic gastroscopy, laboratory tests including routine blood and urine examinations, liver function tests and quantitative determinations of arsenic and fluorine in urine specimens and biopsies of the skin and esophagus were done.

There were 54 males and 11 females, the ratio of male to female being about 5:1. The youngest was 11 years old and oldest 74. Ten cases were 11-20 years old, seven 21-30, eight 31-40, thirteen 41-50, eighteen 51-60, seven 61-70, and two above 70. The mean age was 43. The duration of drinking the well water was 15 years in 45 cases, 11-14 years in 17, and 5-10 years in 3. Sixty-two patients had drunk the well water for more than 10

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years (95.4%). The disease course was 5–10 years in 31 cases, 11–15 years in 23, above 15 years in 5, and unclear in 6. Therefore, the disease course of 28 cases of SEAF (43.1%) was over 10 years.

Clinical manifestations. *Systemic symptoms.* Arthralgia, dizziness, paroxysmal numbness of hands and feet were the most common symptoms in this group. Fatigue, cardiovascular symptoms and itching occurred fairly often (Table).

Systemic symptoms in 65 cases of SEAF

Symptoms	Cases (%)
Arthralgia	41(63.1)
Dizziness	40(61.5)
Numbness of hands and feet	38(58.5)
Fatigue	32(49.2)
Dry mouth	15(23.2)
Cardiovascular symptoms	30(46.2)
Itching	27(41.5)
Weakness	25(38.5)
Thirst	24(37.0)
Cramp	22(38.8)
Digestive symptoms	21(32.0)
Cold extremities	12(18.5)

Physical examination. Generally all the patients were in good condition. Hepatomegaly (up to 2 fingers below the right costal margin) was found in 23 (47.9%) of 48 cases. Thyroids were normal. No Mee's line was found on nails. Muscle tenderness was found in 5 (13.8%) of 36 cases. The pulse of arteria dorsalis pedis was weak or not palpable in 15 (58%) of 26 cases. Raynaud's phenomenon occurred in 19 (48.7%) of 39 cases. Peripheral neuritis presenting as superficial or deep sensory or motor disorder was found in 19 (33.9%) of 56 cases.

Dermatological examination. The skin symptoms of endemic chronic arsenism were manifested as dyspigmentation in 64 cases, (mild 19, moderate 36, and advanced 9), as keratosis in 54 cases (mild 27, moderate 15 and advanced 12),² and as skin tumors in 5 cases. Dyspigmentation of skin commonly

occurred on the trunk, but might occur on extremities and even on mucosa in some advanced cases. In the early stage it was shown as diffuse light-brown pigmented spots mingling with light-white spots in a net-like form. Then it became dark to dark-brown, usually accompanied with keratic maculae or papules. Keratotic lesions generally occurred in palms and soles. Then they would spread to the dorsum of fingers (toes), hands, trunk and even to any part of the extremities, distributed symmetrically. Skin keratosis might be classified as (1) spotting keratosis which presented as hollow keratic spots, like punctate keratosis, (2) corn-like keratosis resembling corns, usually confluent, (3) verruca-like keratosis presenting as verruca vulgaris and (4) skin-horn. Spotting and corn-like keratosis on the palms and soles were typical lesions of arsenic keratosis. Keratic papules on the trunk varied from the size of a grain of rice to a nail, which might protrude from the skin surface with normal or reddish skin color. It might be enlarged into plaques of a nail size with brown or dark-brown color. Skin lesions of different types of keratosis might occur in the same patient. Skin tumors in 5 patients were all confirmed by histopathology. Three of them were basal cell carcinoma presenting as keratic papules on the trunk in a petal form in dark-brown color with a reddish base. They were all superficial pigmented basaloma. One case had both squamous cell carcinoma and Bowen's disease in the scrotum, and another case had Bowen's disease in the groin area.

Stomatologic tests. Dental fluorosis was confirmed in 31 (54.4%) of 57 cases. According to the criteria recommended by the Ministry of Public Health, 3 cases were Grade I, 7 Grade II, 12 Grade III, 4 Grade VI, and 5 unclassified.

Laboratory tests. Blood and urine routine and SGPT done in 42 cases were normal. High level of urine arsenic from 0.09 mg/L

to 0.28 mg/L (normal range 0-0.088 mg/L) was found in 23 of 49 cases involved, and high level of urine fluorine (0.72-4.53 mg/L) was found in 46 cases (normal value 0.6 mg/L for Han residents in Urumqi City).

Special examination. *Radiography.* X-ray of the pelvis and long bones of extremities were taken in 57 patients. Osteofluorosis was found in 53 cases (91.2%). There were three types of osteofluorosis: osteosclerosis, osteoporosis and mixed. The osteosclerosis type was the most common one in this group. Among the 47 cases of osteosclerosis (88.7%), 25 cases had mild and 22 moderate changes. There were 5 cases of osteoporosis type (3 mild and 2 moderate) in this group. One mixed type was mild. None of them had advanced osteofluorosis.

Electrocardiography. Abnormal changes were found in 40 (67.8%) of 57 cases. Early phase repolarization syndrome was encountered in 15, conduction block in 11, arrhythmia in 8, atrial or ventricular hyperplasia in 7, bradycardia in 5, myocardial damage in 5, high voltage of the left ventricle in 4, left deviation in 2, myocardial ischemia in one, decreased Q wave in one and ironing change of ST segment in V_6 in one. Four cases had abnormal changes in 1984, and recovered in 1989. But in most cases there was neither improvement nor deterioration.

Electromyography. Abnormal changes were found in 19 (68%) of 28 patients. The leading manifestation was delay of nervous conduction. Four cases with no symptom or sign of peripheral neuritis were supposed to suffer from subclinical peripheral neuritis.

Fiberoptic gastroscopy. Chronic superficial gastritis was diagnosed in 22 cases. Among them 2 cases were accompanied with peptic ulcer, and one with grade II squamous cell carcinoma of esophagus which was confirmed by histopathology. Another one had

esophageal varices.

Prevention and therapy. Drinking the well water must be stopped as the first step. Since October 1984, water reform has been carried out comprehensively in this area. The water with fluorine content of 0.05 mg/L and arsenic content of 0.045 mg/L was supplied from other areas via underground pipelines into this area.

Examinations after the water reform found that in most cases skin pigmentation decreased and even disappeared, with only light white patches (spots) left. The other symptoms and signs such as keratic skin lesions, neuritis and cardiovascular disorders remained unchanged and improved or deteriorated in a few cases. However, after the water reform these symptoms and signs occurred in a few patients who had not suffered from these disorders previously. Abnormal ECG and osteofluorosis in radiography remained unchanged in most cases, and became normal in a few and deteriorated in some cases. After the water reform, some of patients with associated skin tumors did not develop new lesion, but some patients developed Bowen's diseases and *basalomas*. Four years after the water reform, associated skin basaloma, Bowen's disease and squamous cell carcinoma of esophagus were found each in one case who did not have skin or visceral tumors before.

Application of antedotes. Sodium dimercaptosulfonate (unithiol), 5 ml, was given intramuscularly every day, 4 days a week as a course. Four courses were given continuously. At the same time sodium thiosulfate, 0.64 g, was given intravenously every day for a ten-day course. After this therapy, the arsenic excretion in urine increased notably in moderate and advanced cases. The symptoms were also improved. Keratolytic paste used topically might improve the symptoms of arsenic keratosis. Skin and visceral tumors should be excised as early as possible.

DISCUSSION

There have been many reports on chronic arsenism or fluorosis.²⁻⁴ Each has its own clinical characteristics. We observed that in the endemic area, residents drinking high arsenic and high fluorine water for a long period suffered from combined chronic intoxication of the two trace elements, arsenic and fluorine, which was considered to be a kind of chronic syndrome designated as syndrome of endemic arsenism and fluorosis (SEAF).

The harmful effects of trace elements on human body have aroused the interests of both domestic and foreign investigators. However, the harmful effects on human health of these two trace elements, arsenic and fluorine, in combination have not been reported in the foreign literature.

SEAF presents totally or partially the symptoms of chronic arsenism and chronic fluorosis. We propose that the following should be the diagnostic criteria for SEAF. (1) having drunk high arsenic and high fluorine water for a long period; (2) having the principal signs of chronic arsenism, arsenic keratosis and/or arsenic dyspigmentation; (3) having the principal signs of chronic fluorosis ie, clinical or radiographical manifestations of dental fluorosis and/or osteofluorosis. The subordinate criterion is the increased content of arsenic and fluorine in urine. With the three chief diagnostic criteria, the diagnosis of SEAF may be established. If the subordinate criterion is also met, the diagnosis is definite. All the patients in our series met the three chief diagnostic criteria.

Dermatologic manifestations of SEAF are similar to those of simple chronic endemic arsenism. Skin changes of fluorosis are usually neither evident nor characteristic. Therefore, the skin manifestations of the syndrome are similar to those of chronic

arsenism.

Chronic arsenism is a systemic chronic disease involving almost all the systems. The involvement of the nervous system presents as peripheral neuritis. Fluorine is a kind of protoplasm poison and chronic fluorosis is also a kind of systemic disease, which involves not only bones and teeth, but also most soft tissues. Among the non-osteoporosis damages from fluorosis, the nervous system damage is quite common (10%),^{4,5} presenting as radicular neuritis and spinal cord damages such as paralysis, sensory and sphincter dysfunction. The incidence of peripheral neuritis including subclinical peripheral neuritis in our series was 36.9%, significantly higher than that of simple endemic arsenism or fluorosis in foreign countries. It is worthy of further investigations to find out whether it is due to the synergism of arsenism and fluorosis, which affects the nervous system and aggravates the damage.

In addition, the incidence of cardiovascular disorders is rather high in our patients. Cases with abnormal ECG account for 67.8%. The incidence of cardiovascular disease in simple chronic arsenism was 53.6% in Hotta's report.⁶ Raynaud's phenomenon in our series accounts for 48.7%, but the incidence of Raynaud's phenomenon in simple chronic arsenism is 19-38.8% as reported in the foreign literature. Recently, many domestic investigators have suggested that fluorine has harmful effects on the cardiovascular system, as they have found that fluorine content in the aorta is higher than that in other soft tissues and fluoride can deposit on the arterial wall and promote the progress of arteriosclerosis.⁴ Whether arsenic and fluorine have synergistic effect on the cardiovascular system is also worthy of investigation.

It seems to the authors that no definite conclusion can be reached with regard to the morbidity of associated skin and visceral tumors in SEAF. In our series, the incidence of

associated skin cancer was 7.7% and there was only one case of associated grade II squamous cell cancer of esophagus.

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EARLY RESECTION OF GALLBLADDER AND CHOLEDOCHUS FOUND POSSIBLE TO PREVENT BILIARY-TRACT FROM CANCERIZATION

Congenital cholangiectasis is due to pancreaticocholic confluence abnormality, and most likely leading to biliary-tract cancerization. However, that early resection of gallbladder and choledochus and pancreaticocholic shunt with hepatico-enterostomy can prevent biliary tract from cancerization has been proved recently by the researchers of the Children's Hospital, Shanghai Medical University.

From January 1983 to June 1990, Prof Jin Bai-xiang, et al of the hospital carried out a clinical study of 162 children diagnosed as congenital cholangiectasis by surgery, pathology, etc. The pancreatic and biliary ducts of the patients were morphologically determined by B-ultrasonic technique, operative exploration and intraoperative cholangiography. On this basis, the researchers ob-

served the relationship between pancreaticocholic confluence abnormality and cholangiectasis and so on through animal experiments. The results revealed that almost 100% of the experimented animals with congenital cholangiectasis were complicated with pancreaticocholic confluence abnormality, which is the important pathogenic factor of cholangiectasis and the cause of leading to biliary-tract perforation and / or biliary-tract cancer.

In addition, 18 healthy adult mongrel dogs were selected as controls and made into animal models of pancreaticocholic confluence abnormality, and a modified mutagenic test was used. It was proved that a large amount of pancreatic juice contained in the bile of the patients with pancreaticocholic confluence abnormality is the main predisposing factor for cholangiectasis biliary-tract cancerization. If removal of choledochus and pancreaticocholic shunt are early performed on such patients, cholangiectasis can be effectively treated, and biliary-tract cancerization be prevented.