Hepatic manifestations in chronic arsenic toxicity

AMAL SANTRA, J DAS GUPTA, BINAY K DE,* B ROY, D N GUHA MAZUMDER

Departments of Gastroenterology and *Medicine, Institute of Post Graduate Medical Education & Research, 244 Acharya JC Bose Road, Calcutta 700 020

Objective: **The hepatotoxic action of arsenic, when used as a therapeutic agent, has long been recognized. Data on liver involvement following chronic exposure to arsenic-contaminated water are scanty. We report the nature and degree of liver involvement on the basis of hospital-based and cohort follow-up studies in patients who consumed arsenic-contaminated drinking water for 1 to 15 years.** ***Methods:*** **248 patients with evidence of chronic arsenic toxicity underwent clinical and laboratory examinations including liver function tests and HBsAg status. Liver biopsy was done in 69 cases; in 29 patients, liver arsenic content was estimated by neutron activation analysis. A cohort follow up of 23 patients who took arsenic-free water for 2-12 years was also carried out.** ***Results:*** **Hepatomegaly was present in 190 of 248 patients (76.6%). Noncirrhotic portal fibrosis (91.3%) was the predominant lesion in liver histology. The maximum arsenic content in liver was 6 mg/Kg (mean 1.46 [0.42], control value 0.16 [0.04]; p <0.001); it was undetected in 6 of 29 samples studied. Cohort follow-up studies showed elevation of globulin in four cases and development of esophageal varices in one case.** ***Conclusion:*** **We report the largest number of patients with liver disease due to chronic arsenicosis from drinking arsenic-contaminated water. Noncirrhotic portal fibrosis is the predominant lesion in this population.** [*Indian J Gastroenterol* 1999;18:152-155]

Key words: **Chronic arsenicosis, hepatomegaly, noncirrhotic portal fibrosis, portal hypertension**

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Chronic exposure to inorganic arsenic has been reported to be associated with chronic changes in the liver. Development of ascites has been reported in patients taking liquior arsenic in therapeutic doses for prolonged periods.[1,2] Cases of cirrhosis of liver resulting from continued use of Fowler's solution containing potassium arsenite have also been described.[3] However, when liver biopsies of 44 psoriatic patients receiving potassium arsenate and 37 similar patients receiving no drug were compared, no histological differences were found.[4] Portal hypertension without signs of cirrhosis of liver has subsequently been reported following chronic arsenic medication, mostly as Fowler's solution.[5-11] Some of those patients also had typical skin manifestations.

Drinking of arsenic-contaminated water was first suspected to cause noncirrhotic portal hypertension in two patients from Chandigarh.[12] A large number of patients suffering from chronic arsenic toxicity due to drinking of arsenic-contaminated tubewell water have been attending our institute since 1983. This led us to carry out a systematic study on the problem of liver disease caused by chronic intake of arsenic through drinking water. Some results of our study have been published previously.[13,14,15] The current presentation is a compilation of our data between 1985 and 1998.

Methods

A total of 248 consecutive patients with evidence of chronic arsenic toxicity attending the arsenic clinic and medical out patients department of our hospital were studied. The inclusion criteria were as follows: (1) typical raindrop pigmentation and/or depigmentation of the skin of the body and limbs, (2) thickening of palms and soles with or without nodules in those areas characteristic of chronic arsenic toxicity and (3) arsenic level above the permissible limit set by the WHO (>0.05 mg/L) in the water consumed by these people. The exclusion criteria were (1) past history of malaria or kala-azar, (2) prolonged intake of a hepatotoxic drug or alcohol, (3) hematological disease, and (4) cardiovascular or metabolic disease.

The arsenic-contaminated water (0.05-3.2 mg/L) which the subjects drank was drawn by hand pump from subsoil water at varying depths. The patient population also included 20 cases from southern Calcutta who took water containing high quantities of arsenic (5.05-14.2 mg/L) due to contamination of subsoil water by the waste of a factory manufacturing Paris green (copper acetoarsenite). None of these patients gave any history of taking arsenic-contaminated food. The duration of intake of contaminated water usually varied from 1 to 15 years, but in some cases it was life-long.

In addition to a thorough clinical examination, blood counts, blood biochemistry and examination of urine and stool were performed. Upper gastrointestinal (GI) endoscopy could be done on 73 patients with splenomegaly. Liver biochemistry and viral markers for HBsAg (ELISA) were carried out in 93 cases who could be admitted in the hospital. Liver biopsy was carried out in 69 of these patients who consented. The degree of portal fibrosis was graded[13] as: grade I - mild fibrosis producing expansion of portal zone; grade II - expansion of portal zone with thin fibrous extension producing septae; grade III - moderate fibrosis in the portal zone with thick septae; grade IV -

Table 1: Clinical characteristics of 248 patients with chronic arsenicosis

Presenting features	No. of patients	Percentage
Rain-drop pigmentation	234	94.4
Weakness	163	65.7
Keratosis (sole/palm)	162	65.3
Dyspepsia	165	66.5
Cough	154	62.1
Burning sensation of eyes	74	29.8
Anemia	109	44.0
Hepatomegaly	190	76.6
Splenomegaly	73	29.4
Varices (n=73)	5	
Ascites	5	2.0
Crepitation ± rhonchi	75	30.2
Polyneuropathy	20	8.1
Pedal edema	23	9.3
Blackfoot disease (gangrene)	3	1.2
Skin cancer	5	2.0

Twenty-three subjects who consumed arsenic-free water (<0.01 mg/L) obtained from deep tubewells were followed up for a period of 2-12 years. (Five of them had been treated with d-penicillamine 250 mg QDS for 15 days as part of another study on the effect of chelation). Detailed clinical examination, liver biochemistry and upper GI endoscopy were repeated in each case. Repeat liver biopsy could be done in four cases, including two who had received d-penicillamine.

Results

The 248 patients included 193 men, with mean (SD) age 32.5 (13.4) years. The clinical manifestations in these cases are given in Table 1. The liver was palpable 2-6 cm below the costal arch in 190 (76.6%) cases, and the spleen 1.5-8 cm below the costal arch in 73 (29.4%) patients; ascites was present in 5 cases. Varices were present in five cases (three of them had no history of GI bleed).

Results of liver profile in 93 patients with firm hepatomegaly are given in Table 2. Elevated ALT (>40 IU/L), AST (>40 IU/L) and alkaline phosphatase (ALP; >400 IU/L) were detected in 24 (25.8%), 57 (61.3%) and 27 (29.0%) cases, respectively. Serum globulin level was high (>3.5 g/dL) in 19 (20.7%) cases.

Table 2: Liver biochemistry of 93 patients with chronic arsenicosis

	Range (IU/L)	Mean (SD) (IU/L)
Bilirubin (mg/dL)	0.4-1.1	0.7 (0.2)
Albumin (g/dL)	2.0-5.5	4.3 (0.7)
Globulin (g/dL)	1.8-5.0	3.1 (0.7)
ALT (IU/L)	16-208	38.8 (29.0)
AST (IU/L)	20-144	54.8 (30.6)
ALP (IU/L)	78-1206	295.5 (196.5)

dense fibrosis within the liver with a tendency to pseudolobulation. Arsenic level in liver tissue was detected by neutron activation analysis;[13] its concentration in water was estimated by atomic absorption spectrophotometry.[16]

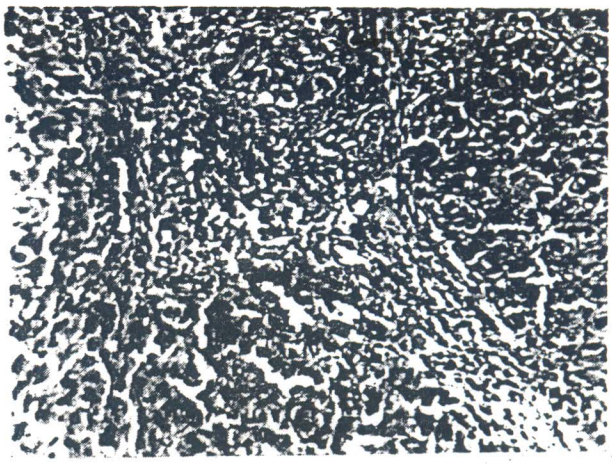

Fig 1: Liver histology showing gross fibrosis with tendency to pseudolobule formation. The markedly expanded portal zone contains multiple vascular channels (H & E, 400 X).

Liver histology showed portal fibrosis in 63 (91.3%) cases, cirrhosis in 2 cases (2.9%) and normal picture in 4 (5.8%) cases. Sera of the two patients with cirrhosis tested positive for HBsAg. The portal fibrosis was characterized by expansion of portal zones of varying degrees. Fibrous extension from the portal tracts into the liver lobules producing septae was found in some cases. At some regions the expanded portal zone contained a leash of vessels replacing the portal vein branches (Fig 1). The degree of fibrosis in the liver (Fig 2) was mild in most patients (grade I in 34 [53.9%], grade II in 19 [30.2%]); moderate to severe fibrosis was observed in only a few cases (grade III in 6 [9.5%] and grade IV in 4 [6.3%]).

The maximum arsenic content in the liver was 6 mg/Kg (mean 1.46 [0.42]; control 0.16 [0.04]; $p < 0.001$); it was undetected in 6 of 29 samples. The arsenic content of

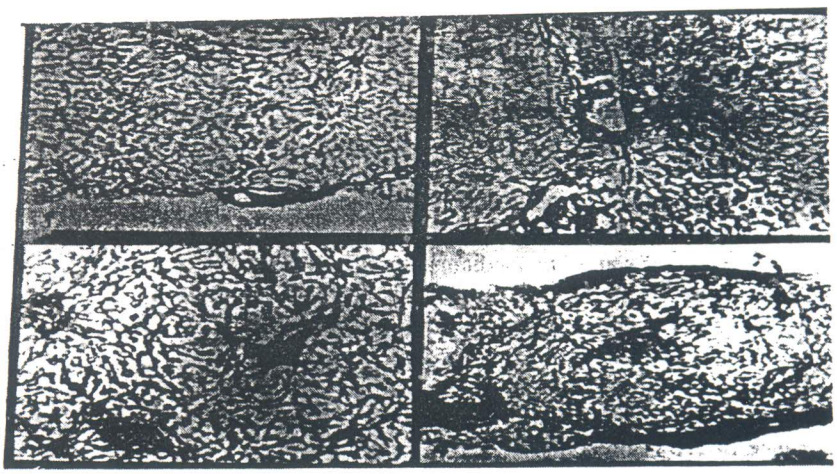

Fig 2: Chronic arsenicosis showing (1) grade I, (2) grade II, (3) grade III, (4) grade IV fibrosis in liver (reticulin stain, 400X)

liver tissue did not correlate with the degree of hepatic fibrosis or with the arsenic content of the water consumed.

Follow up of 23 subjects drinking arsenic-free water showed significant elevation of serum globulin level in 9 cases (as compared to 5 cases when tested initially). There was no difference in the level of ALT, AST and ALP. Esophageal varices (grade II) were detected in one case during follow-up study. Repeat liver biopsy done in four cases showed no change in grade of liver fibrosis.

Discussion

Most reports of chronic arsenic exposure focus on skin manifestations. Sporadic reports of liver involvement following intake of inorganic arsenic in medicinal form are available. A few reports mentioned the lesion to be noncirrhotic. Two cases reported by Datta *et al*[12] and our data of 13 and 45 cases[13,14] suggest that noncirrhotic portal hypertension is common in chronic arsenic toxicity. Of 15 cases of chronic arsenicosis described by Nevens,[11] 11 were caused by application of Fowler's solution. All the cases in our study were drinking subsoil water which had arsenic above permissible level (>0.05 mg/L). Hepatomegaly was observed in a high percentage (76%) of our cases. Most authors report liver profile to be normal or near normal in chronic arsenicosis with liver involvement. We observed elevated levels of AST, ALT, ALP and globulin in 25.7%, 61%, 27% and 20.7% of cases with hepatomegaly, respectively.

Of 73 cases with splenomegaly, esophageal varices were found in only 5 cases. A majority of patients thus had no definite evidence of portal hypertension though portal zone fibrosis was seen in liver biopsy in most of them. Portal hypertension was observed by Nevens *et al*[11] in 7 of 8 cases with chronic arsenicosis and a history of variceal bleeding.

The features of periportal fibrosis and multiple vascular channels in expanded portal zones observed in our study are similar to those observed in noncirrhotic portal fibrosis/idiopathic portal hypertension.[5,8,9,12,13] Franklin *et al*[3] reported periportal fibrosis with intralobular extension in one of three cases of arsenic toxicity they studied. Extension of fibrosis from portal tracts or tendency to pseudolobule formation that we observed in our cases were not noted by Morris *et al*[8] in their patients with noncirrhotic portal hypertension caused by medicinal arsenic. The pathogenesis of portal hypertension in chronic arsenicosis thus appears to be similar to that of noncirrhotic portal fibrosis; there appears to be no difference in their hepatic histology. We observed only two patients with cirrhosis of the liver among the patients studied; both these patients had evidence of HBV infection.

In the cohort follow-up study, esophageal varices were detected in a patient who did not have them earlier and globulin levels were elevated in more cases over time; these suggest that hepatic fibrosis caused by arsenic is progressive.

Early investigators described a few cases of chronic liver disease due to drinking of arsenic-contaminated beer[17,18] or water or medicinal arsenic in the form of Fowler's solution. More recently, there have been reports of chronic arsenic toxicity in the form of arsenical dermatosis or skin cancer due to drinking of arsenic-contaminated water.[19-24] There is no report of involvement of the liver as a major clinical problem from any of these areas. The present report is the largest series showing significant involvement of the liver in the form of noncirrhotic portal fibrosis and portal hypertension among people drinking arsenic-contaminated water for a prolonged period.

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Correspondence to: Dr Guha Mazumder

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