Pulmonary Involvement in Chronic Arsenic Poisoning from Drinking Contaminated Ground-water

BK De, D Majumdar**, S Sen, Supriya Guru, S Kundu

Abstract

Objectives: Chronic arsenic poisoning, due to ingestion of contaminated ground-water, is a major public health problem in West Bengal. It causes multiorgan damage. The present study attempts to objectively investigate the pulmonary involvement by examining the lung function. The nature of lung changes was also evaluated.

Material and Methods: One hundred and seven subjects with (cases) and 52 subjects without (controls) chronic arsenic poisoning were examined by spirometry. Forced expiratory volume-1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR) were measured. Bronchoalveolar lavage (BAL) was performed in five cases with and five cases without pulmonary involvement.

Results: Thirty three (30.8%) cases and four (7.6%) controls (p<0.01) had respiratory involvement. The pattern of involvement in cases was: obstructive- 20(68.9%) (including three (10%) with bronchiectasis), restrictive- 1(3.5%), mixed- 8(27.6%), malignancy- 4(12.1%)(adenocarcinoma- 1, squamous cell- 2, undifferentiated- 1). FEV1 (69.7±25.9 [n=105] vs 83.7±15.19 [n=51], p=0.0005), FVC (77.4±22.7 [n=105] vs 85.6±18.23 [n=51], p=0.025), FEV1/FVC (73.6±13.38 [n=105] vs 79.1±18.65 [n=52], p=0.007) and PEFR (53.9±21.52 [n=103] vs 67.3±18.36 [n=51], p=0.0002) (percent of predicted) were all reduced more in cases compared to controls. Worsening of these parameters correlated with increasing degree of arsenic toxicity. Markers of inflammation (macrophage, lactate dehydrogenase, nitric oxide) were apparently more in the BAL fluid of those with lung involvement than in those without, though the arsenic content did not differ significantly.

Conclusion: Chronic arsenic poisoning causes pulmonary involvement, predominantly obstructive, the degree of which worsens with increasing degree of arsenic toxicity. Inflammation, rather than direct toxicity, appears to be the underlying mechanism.

INTRODUCTION

Chronic arsenic poisoning due to contaminated ground water, which is a major source of drinking water, is an important form of xenobiotic insult, which has assumed worldwide importance over the past three decades. One of the worst afflicted areas is south-east Asia, mainly Gangetic West Bengal and Bangladesh, where contaminated shallow tube well water is responsible for the problem. A population of about 40 million is at risk in West Bengal alone. Multisystemic involvement in this condition has been well established, including mucocutaneous, cardiovascular, neurological and hepatic disorders, along with malignant changes.11

Pulmonary involvement has been reported by some workers. Increased mortality from lung cancer associated with chronic arsenic poisoning has been reported from Taiwan, Chile and Argentina, while a study from Chile suggested an association with non-malignant respiratory changes. Another report showed the presence of pulmonary fibrosis in two out of five autopsies performed on children dying of chronic arsenicosis. A recent epidemiological survey in West Bengal found clinical evidence of respiratory effects due to chronic arsenic poisoning.

However, none of these studies systematically investigated the lung functions, and nature of lung changes, in these patients. Therefore, this is what we have attempted to evaluate in the present study, and compared them with arsenic-unaffected controls. Broncho-alveolar lavage (BAL)
fl uid was studied in a few of them, to try to gain a better insight into the underlying pathophysiology.

**MATERIALS AND METHODS**

One hundred and forty three patients of chronic arsenic poisoning from rural areas of agriculture based population of our state (between the ages of 15 and 50 years) were selected consecutively for this study from the Arsenic Clinic of SSKM Hospital / IPGME&R, Calcutta, from June 1999 to October 2000. Approval for the study protocol was obtained from the institutional ethics committee, and written consent was taken from all patients. Only those patients who fulfilled at least two of the following three criteria for chronic arsenic poisoning (modified from previously used criteria to make inclusion more stringent) were included: (a) evidence of drinking water with an arsenic level >0.05 mg/L for at least 3 years, (b) presence of raindrop mottled skin pigmentation (trunk, limbs) with or without palmoplantar hyperkeratosis, (c) hair or nail arsenic level above control values (hair: 0.15±0.35 µg/gm, nail: 0.34±0.25 µg/gm). Arsenic content of drinking water, hair and nail were estimated in the Department of Chemistry of School of Tropical Medicine, Calcutta by hydride generation atomic absorption spectrophotometry (HGAAS) method in the Perkin Elmer Atomic Absorption Spectrophotometry machine (Perkin Elmer Corp., Norwalk, CT, USA).

**Exclusion criteria**

All cases with a history of smoking, asthma, environmental (other than arsenic exposure) or occupational lung disease, active or past pulmonary tuberculosis or cardiovascular disease were excluded. Ultimately, 107 cases were retained in the study protocol.

**Assessment for arsenic toxicity**

Severity of arsenic poisoning was determined in all cases by a ‘clinical score’ (maximum-33), including a ‘cutaneous score’ (maximum-6), after a thorough clinical evaluation. A careful history was taken to determine the duration of intake of arsenic contaminated water (assuming stable levels of arsenic contamination in the water since the digging of the wells concerned).

**Selection of controls**

Adopting the same exclusion criteria 52 out of 87 persons (age between 15 and 50 years), who did not have any evidence of chronic arsenic poisoning and who were drinking uncontaminated water were taken as control. They were selected consecutively from the list of persons (neighbors; from address) of same geographic area from rural population coming to test their water sample for arsenic content at School of Tropical Medicine; Chemistry Department. They were further investigated (outlined below) after taking written consent.

**Pulmonary assessment**

All cases and controls underwent a clinical respiratory evaluation (including a thorough history) and were also investigated by sputum examination on three consecutive days (for acid-fast bacilli) and chest X-ray (postero-anterior view) in all. A clinical diagnosis of chronic bronchitis was made using the criteria of the American Thoracic Society.

**Pulmonary function test (PFT)**

All cases and controls underwent pulmonary function testing by a Microlab 3300 (Micro Medical Ltd., Rochester, England) pulmonary function testing machine. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were assessed and the FEV1/FVC ratio was calculated. Peak expiratory flow rate (PEFR) was also measured. Three readings were taken, and the one with the best performance was selected for each subject. Normal values were taken as ≥ 80% for FEV1, ≥ 80% for FVC and ≥ 70% for FEV1/FVC (all expressed as percentage of predicted value), based on our laboratory’s normal values (based on a sample of healthy individuals without lung disease from the local population).

Obstructive pattern was recognized by (i) FEV1 <80% and (ii) FEV1/FVC <70%. Severity was categorized as normal (FEV1/FVC >69%), mild (61-69%), moderate (45-60%) and severe (<45%).

Due to lack of facilities, total lung capacity could not be measured.

**Bronchoscopy**

After taking informed written consent, bronchoscopy (using a flexible fibre-optic bronchoscope [Olympus BF type IT-30, Tokyo, Japan]) was performed in 10 cases of chronic arsenicosis, five with and five without pulmonary involvement. Broncho-alveolar lavage (BAL) was done with normal saline. Arsenic content of the BAL fluid was estimated by HGAAS method. Also, lactic acid dehydrogenase (LDH) levels, macrophage counts (by hemocytometry) and nitric oxide (NO) levels were estimated in the BAL fluid. The nitrite concentration in the culture medium (RPMI) was measured, as an indicator of NO production, by the Greiss reaction. 500 µL of each supernatant was mixed with the same volume of Greiss reagent (1% sulfanilamide in 5% phosphoric acid and 0.1% naphthylethylenediamine dihydrochloride in water). Absorbance of the mixture at 550 nm was determined by spectrophotometry (Hitachi, Tokyo, Japan). The concentrations of nitrite were determined by comparison to a standard curve constructed using sodium nitrite ranging from 3 to 100 µM.

**Other investigations**

All cases and controls also underwent routine investigations, including complete hemogram, urinalysis and liver function tests (including enzymes). Four of the cases with restrictive / mixed pulmonary changes, and one with a clinical suggestion of bronchiectasis, were also investigated by high resolution computed tomography (HRCT) of the chest. Also, those cases whose chest X-rays showed a suspicious opacity suggesting lung malignancy were subjected to ultrasound- or CT- guided fine needle aspiration cytology (FNAC), and, in one patient who underwent lobectomy, histopathological examination of the specimen was performed.
Statistics

Results were expressed as mean ± standard deviation. ‘Correlation and regression’, ‘chi-square test’ and ‘single factor: ANOVA’ were used as required. ‘P’ < 0.05 was considered statistically significant. Results were analyzed using Microsoft Excel software (Microsoft Corp., Redmond, WA, USA).

RESULTS

One hundred and seven cases with and 52 controls without chronic arsenic poisoning were studied. Among cases, mean water arsenic content was 0.55±0.47 mg/L (n=84), which was being consumed for a mean duration of 17.31±7.83 years (n=103). Hair and nail arsenic levels were respectively 3.25±2.53 µg/gm (n=50) and 4.93±5.46 µg/gm (n=47). Mean clinical and cutaneous scores were respectively 8.9±2.93 and 3.38±1.53 (n=106). The demographic profile and lung functions of cases and controls are given in Table 1. All parameters of pulmonary function were significantly worse among cases.

Thirty three out of 107 cases of chronic arsenic poisoning had evidence of pulmonary involvement. They were significantly older, with significantly higher clinical and cutaneous scores, and were consuming water with a higher arsenic content as compared to those without lung involvement (see Table 2). However, duration of water intake, hair or nail arsenic levels did not differ significantly between the two groups.

Out of 29 cases with non-malignant lung disease, 20 (68.9%) cases had obstructive pattern of lung involvement (mild: 7; moderate: 9; severe: 4), eight (27.6%) cases had mixed obstructive-restrictive pattern and only one (3.5%) had pure restrictive involvement. On the basis of clinical evaluation, chest X-ray in all cases and, in five cases, HRCT scan of the chest, the patients were diagnosed to have chronic obstructive pulmonary disease (COPD) in 17 (58.62%), bronchiectasis in three (10%) and interstitial lung disease, early or late, in nine (31.2%) cases (Fig.1) (diagnosis was done by HRCT in four and rest five cases from chest radiography). Four out of the 33 cases (12.1%) were diagnosed to have bronchogenic carcinoma (adenocarcinoma-1, squamous cell carcinoma-2, undifferentiated carcinoma-1). Of these, one had normal lung function while another showed moderate obstruction (FEV1/FVC= 48%). The other two were too debilitated to undergo lung function testing. For the diagnosis of ILD, we followed (restrictive lung disease) with chest x-ray finding and in some cases we did HRCT of chest.

Both cutaneous and clinical scores showed a strong negative correlation with all parameters of pulmonary function (Table 3, Fig.2). Duration of water intake correlated relatively weakly with all the parameters, but had a significant negative correlation with PEFR. While hair or nail arsenic levels did not correlate with any pulmonary function parameter, water arsenic content showed a significant negative correlation only with FEV1.

Table 1: Demographic profile and pulmonary function of cases (chronic arsenic poisoning) and controls

<table>
<thead>
<tr>
<th></th>
<th>Case (n=107)</th>
<th>Control (n=52)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.1±11.04</td>
<td>33.7±11.71</td>
<td>0.78</td>
</tr>
<tr>
<td>M:F</td>
<td>81:26</td>
<td>36:16</td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>77.4±22.7</td>
<td>85.6±18.23</td>
<td>0.025</td>
</tr>
<tr>
<td>FEV1/FVC(105,51)</td>
<td>69.7±25.9</td>
<td>83.72±15.19</td>
<td>0.0005</td>
</tr>
<tr>
<td>FVC (105,51)</td>
<td>77.4±13.38</td>
<td>79.1±18.65</td>
<td>0.007</td>
</tr>
<tr>
<td>PEFR(105,52)</td>
<td>53.9±21.52</td>
<td>67.3±18.36</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>33(30.8%)</td>
<td>4(7.6%)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

(all pulmonary function values as percent of predicted)

<table>
<thead>
<tr>
<th></th>
<th>Lung change (n=33)</th>
<th>No lung change (n=74)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>39.2±9.81</td>
<td>32.2±10.40</td>
<td>0.001</td>
</tr>
<tr>
<td>M:F</td>
<td>22:11</td>
<td>59:15</td>
<td></td>
</tr>
<tr>
<td>Cutaneous score (µg/gm)</td>
<td>4.6±1.17</td>
<td>2.8±1.34 (73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical score (µg/gm)</td>
<td>11.1±2.61</td>
<td>7.7±2.40 (73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of intake (yrs)</td>
<td>19.1±7.74</td>
<td>16.5±7.77 (70)</td>
<td>0.1</td>
</tr>
<tr>
<td>Water As content (mg/L)</td>
<td>0.77±0.47 (30)</td>
<td>0.42±0.42 (54)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Hair As level(µg/gm) (n)</td>
<td>3.88±2.72 (21)</td>
<td>2.79±2.32 (29)</td>
<td>0.13</td>
</tr>
<tr>
<td>Nail As level(µg/gm) (n)</td>
<td>5.9±±3.81 (19)</td>
<td>4.2±±6.32 (28)</td>
<td>0.3</td>
</tr>
<tr>
<td>FEV1 (n)</td>
<td>39.9±20.43 (31)</td>
<td>82.2±15.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC (n)</td>
<td>54.8±20.34 (31)</td>
<td>87.0±15.99</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1/FVC (n)</td>
<td>60.1±15.78 (31)</td>
<td>79.7±6.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PEFR (n)</td>
<td>34.1±19.48 (31)</td>
<td>62.5±16.01 (70)</td>
<td>&lt;0.0001</td>
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(see Table 2. Clinical, arsenic exposure and pulmonary function profiles compared between patients of chronic arsenic poisoning with and without pulmonary involvement)

Table 2: Clinical, arsenic exposure and pulmonary function profiles compared between patients of chronic arsenic poisoning with and without pulmonary involvement

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<td>FEV1- Forced expiratory volume in 1 second</td>
<td>39.2±9.81</td>
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<td>0.001</td>
</tr>
<tr>
<td>FVC- Forced vital capacity</td>
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<td>59:15</td>
<td></td>
</tr>
<tr>
<td>PEFR- Peak expiratory flow rate</td>
<td>4.6±1.17</td>
<td>2.8±1.34 (73)</td>
<td>&lt;0.0001</td>
</tr>
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(all pulmonary function values as percent of predicted).

Fig. 1: High resolution computed tomography of the chest showing septal thickening with interstitial fibrosis.
The toxicological mechanism underlying the pulmonary manifestations of chronic arsenic poisoning is not clear at present. Some workers have reported a high lung concentration of arsenic, in mummies (from Chile), in two cases after acute arsenic poisoning, and in autopsies of copper smelters. Due to ethical reasons, we have been unable to examine lung tissue for accumulated arsenic. However, we have studied the BAL fluid of a small number of these cases. Though no obvious relation with BAL fluid arsenic level could be demonstrated, markers of inflammation (including LDH level, macrophage count and macrophage nitric oxide activity) were more in those with lung involvement than in those without. Though only a very few cases were thus investigated, it perhaps indicates an inflammation-mediated immunological basis of the lung changes seen in chronic arsenic poisoning, rather than a direct toxic effect of the element itself. This is in keeping with our findings in hepatic fibrosis associated with arsenic poisoning, where the arsenic content of the liver tissue did not correlate with the degree of hepatic fibrosis. This might account for the obstructive changes, and also may lead to interstitial lung disease due to its fibrogenic potential.

The inflammatory basis of pulmonary changes in chronic arsenic poisoning is associated with pulmonary diseases. While obstructive pattern was the predominant change observed, restrictive pattern was also noted in a few. Chronic obstructive pulmonary diseases accounted for the largest group of patients, followed by interstitial lung disease, malignancies and bronchiectasis. This is in keeping with the findings of Hotta, who observed chronic bronchitis among 52.3% of his patients of arsenic poisoning along with bronchiectasis and pulmonary fibrosis in some. Another study, a community-based one from our centre, also observed respiratory effects in these cases. However, none of these studies systematically investigated the lung functions of patients, which we have tried to do to make our assessment of the respiratory system more objective, and to evaluate any relation between the degree of arsenic poisoning and the extent of pulmonary involvement. Although it is a clinic base (cases) study still it will represent a good approximation of population based design as primary control (neighbors) chosen from same rural agriculture-based population of non-clinic control. What future community-based studies need to do is to try to identify any confounding factors which might cause lung changes and which are associated with drinking water from the arsenic-contaminated wells.

Analysis of the BAL fluid (Table 4) was performed in 10 cases of arsenic poisoning, including five with and five without pulmonary involvement. Such small numbers did not permit any valid statistical analysis, but apparent examination of the data reveals nearly equal arsenic content of the fluid in both groups, though markers of inflammation (including LDH levels, macrophage counts and NO levels) were distinctly more apparent in the samples from those with pulmonary involvement.

Among the 52 controls, only four had evidence of respiratory disease. All four had obstructive changes, with predominant chronic bronchitis in two and mixed bronchitis-emphysema in two patients.

**DISCUSSION**

It is evident from our study that chronic arsenic poisoning is associated with pulmonary diseases. While obstructive pattern was the predominant change observed, restrictive pattern was also noted in a few. Chronic obstructive pulmonary diseases accounted for the largest group of patients, followed by interstitial lung disease, malignancies and bronchiectasis. This is in keeping with the findings of Hotta, who observed chronic bronchitis among 52.3% of his patients of arsenic poisoning along with bronchiectasis and pulmonary fibrosis in some. Another study, a community-based one from our centre, also observed respiratory effects
arsenic poisoning has been previously suggested in studies with rat models. Increased activation of pulmonary macrophages,25,26 as well as increased production of mediators of inflammation (like tumour necrosis factor alpha, interleukin-1, LDH)25 have been observed.

Bronchiectasis was found in 10% of our lung cases. This might be related to the observation of Hotta that, in chronic arsenic poisoning, the respiratory tract seems to become easily infected.11 A chronically inflamed bronchial mucosa might account for this susceptibility to infection.

Since the late 1980s, arsenic has been recognized as a carcinogen by the International Agency for Research on Cancer27 as well as the Environment Protection Agency, USA.28 The occurrence of lung cancers was fairly high (3.7%) among our 107 cases of arsenic poisoning, accounting for 12.1% of all lung diseases. This might be due to the fact that all the cases were selected from our institute, which is the tertiary referral center for arsenic poisoning in eastern India. On the other hand, an even higher occurrence of lung malignancy (8.8%) has been reported among patients of environmental/occupational arsenic poisoning from Japan.11

The diagnosis of restrictive/mixed pattern of pulmonary involvement could have been made much more definitively if total lung capacities could have been measured. Unfortunately, as already mentioned, this could not be done due to lack of facilities.

It would also have been more helpful if HRCT scan of chest and bronchoscopy were performed in a larger number of patients. This was however not possible due to logistic problems, and, in case of bronchoscopy, due to the invasive nature of the study as well as lack of consent in many.

In conclusion, the present study demonstrates that chronic arsenic poisoning from drinking arsenic contaminated water is associated with pulmonary diseases, predominantly of the obstructive variety, though restrictive and malignant changes also occur. This might be a bit surprising, as one toxin would be expected to cause only one type of change, but many established lung carcinogen like smoking, asbestos and silica may produce both malignant and non-malignant lung changes. Moreover, silicosis may produce impairment of lung function like obstructive, restrictive or a combination of both29,30 All parameters of respiratory function worsen significantly with worsening degree of arsenic poisoning. Finally, inflammation, rather than direct toxicity by the element itself, seems to be the mechanism underlying lung damage. This is something that future studies will perhaps have to investigate.

REFERENCES


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**Announcement**

**Training in Diabetes Foot Care**

Project funded by the World Diabetes Foundation (WDF)

**Academic Support by:**
- Consultative section on the diabetic foot - International Diabetes Federation (IDF)
- International Working Group on the Diabetic Foot (IWGDF)
- Diabetic Foot Society of India (DFSI)
- Muhimbili University and College of Health Sciences (MUCHS), Dar es Salaam, Tanzania

**Project Committee:**
- Sharad Pendsey, India; Karel Bakker, The Netherlands; Ali Foster, U.K.; Zulfiqarali Gulam-Abbas, Tanzania; Vijay Vishwanathan, India

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1. Basic Course: 2 days at four centers in India (Kolkata, New-Dehli, Mumbai & Chennai). Each center will have 25 doctors & 25 paramedics. The course is likely to be held between September/October 2004.
2. Advanced Course: 2 days (after 1 year) for the same participants is mandatory

**Faculty: Experts in the field of Diabetic Foot Care**

Selected participants will be provided with excellent educational material along with diagnostic/therapeutic instrument kits. Travel to nearest venue, lodging & boarding, access to training and resource materials are covered by a grant from WDF Certificate of participation on completion of the advanced course. Preference to postgraduates, coming from private/public/corporate/govt. medical institutions. Opportunity to start Preventive Diabetes Foot Care Clinic.

**Selection committee’s decision will be binding on all applicants.**

The last date of receipt of application is 30th June 2004.

*Write for application form to*

**Dr. Sharad Pendsey**

Project Incharge, Diabetes Clinic & Research Center

“Shreeniwas”, Opp.Dhantoli Park, Nagpur 440 012 (India)