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Sensory disturbance and electrophysiological findings in patients with chronic arsenic intoxication in Toroku, Japan: A 40-year follow-up study

Nobuyuki Ishii[1], *Hitoshi Mochizuki[1], Yuka Ebihara[1],
Kazutaka Shiomi[1], Masamitsu Nakazato[1]

1 Division of Neurology, Respirology, Endocrinology and Metabolism,
Department of Internal Medicine, University of Miyazaki, Japan

Abstract

Chronic arsenic intoxication is known to cause multisystem impairment including sensory dysfunction, and is still a major threat to public health in many countries. In Toroku, a small village in Japan, arsenic mines operated from 1920 to 1962, and residents suffered serious sequelae of chronic arsenic intoxication. We have performed annual medical examinations of these patients since 1974, allowing us to characterize patients' long-term health following their last exposure to arsenic. We have evaluated the longitudinal analysis of sensory dysfunction by neurological examination and nerve conduction study. The severity of both superficial and deep sensation worsened significantly over time ($P = 0.04$ and $P < 0.01$, respectively), although nerve conduction velocities of sensory nerves in the lower extremities significantly improved ($P < 0.01$). This is the first study characterizing the longitudinal sequelae of sensory impairment after chronic arsenic exposure. Our study will be helpful in assessing the prognosis of patients worldwide who still suffer from chronic arsenic intoxication.

Keywords: Arsenic, chronic arsenic intoxication, neurological findings, electrophysiological study

1. Introduction

Arsenic intoxication is known to cause multisystem impairment, either acutely or chronically depending on the level of arsenic exposure (Abdul et al. 2015). Chronic arsenic toxicity, which is due to low-concentration exposure over a long period of time, impairs the same organs and tissues as acute toxicity, although skin and nervous system disturbances are usually more pronounced (Naujokas et al. 2013).

In Toroku, a small village in a narrow valley in Miyazaki prefecture, Japan, arsenic mines were in operation from 1920 to 1962, except for several years around 1945 because of World War II. Arsenic was roasted at a refinery without a dust-collecting system. Thus, huge amounts of arsenic trioxide-containing gases were leaked from the roasters and intermittently covered the entire Toroku valley, causing both refinery workers and residents be exposed to arsenic orally (via contaminated food and water), dermally, or tracheally (via contaminated air) (Miyazaki prefecture 1972; Tsuda et al. 1990). The polluted environment caused chronic arsenic intoxication in many workers and residents, leading to many deaths before 1962 (Miyazaki prefecture 1972; Mochizuki et al. 2016). In 1972, 10 years after the mine closed, arsenic concentrations were finally measured by Miyazaki prefecture. Extremely high arsenic content (200–8,000 mg/kg) was detected from the dust of ceiling boards of residences near the mine, and the average arsenic concentrations in neighboring soil and in water percolating

Contact: Hitoshi Mochizuki, MD, PhD, University of Miyazaki
5200 Kihara, Miyazaki, 889-1692, Japan
mochizuki-h@umin.net, +81-985-85-2965

from the slag were 2,760 mg/kg and 180 mg/L, respectively. In the resident bodies, high concentrations were also found in the hair (average concentration, 1.52 mg/kg; n = 29), claw (10.83 mg/kg; n = 31) and urine (0.58 mg/L; n = 38) (Miyazaki prefecture 1972; Hotta et al. 1979), presumably because many residents had continued to drink the contaminated water from Toroku River after air exposure had ceased. Beginning in 1974, surviving residents underwent the annual Toroku Medical Examination, allowing us to obtain more than 40 years of longitudinal information about the clinical characteristics of chronic arsenic intoxication.

To date, there have been no reports describing the long-term history of patients who are no longer exposed to arsenic; most previous studies have been cross-sectional, and patients were still actively exposed to arsenic. Here, we conducted the following investigations in Toroku patients with chronic arsenic intoxication after exposure cessation: a longitudinal analysis of sensory dysfunction based on physical examination and neurophysiological methods.

2. Materials and methods

2.1 Patients

All patients enrolled in this study lived within 1000 m from the mine roaster prior to 1962, had typical symptoms and signs of arsenic poisoning, such as dermatological (pigmentation or keratosis) or neurological disturbances (peripheral neuropathy), and were diagnosed with chronic arsenic exposure by the government after 1974, when administration of the Toroku Medical Examination began.

This study protocol was approved by the Ethics Committee of the University of Miyazaki, with a waiver of written informed consent obtained from patients with chronic arsenic exposure, and was carried out in accordance with the Declaration of Helsinki.

2.2 Evaluation of sensory dysfunction

We evaluated sensory impairment with a sharp toothpick for pain, test tubes containing water at 0°C or 50°C for temperature, soft tissue paper for touch, and a 128 Hz tuning fork for vibration. The severity of sensory disturbances was graded as follows: "0," almost normal sensation; "1," sensation decreased by less than half; and "2," sensation decreased by more than half.

2.3 Longitudinal study of sensory dysfunction

To evaluate long-term sensory dysfunction by neurological examination, we selected patients who had undergone the Toroku Medical Examination over 10 times for more than 10 years. For nerve conduction studies (NCS), which were first conducted in 2003, we enrolled patients if they had undergone NCS more than three times. For both types of analysis, patients were excluded if they had diabetes mellitus, alcoholism, or a past history of gastric resection.

2.4 NCS protocol

NCS were conducted using a Neuropack MEB2200 electromyogram apparatus (Nihon Kohden, Tokyo, Japan). Motor NCS were performed on the median and tibial nerves. The stimulus site was 3 cm proximal to the wrist crease and elbow in median nerve studies, and just lateral to the medial malleolus and popliteal fossa in tibial nerve studies. Antidromic sensory NCS were conducted on the median and sural nerves. In the median nerve study, the recording site was the index finger with the stimulation at the wrist, and in the sural nerve study, the recording site was the lateral malleolus with stimulation 14 cm proximal to the mid-calf.

2.5 Statistical analysis

Categorical variables are shown as percentages (%) whereas continuous variables are shown as medians (25th–75th percentiles). The Fisher's exact test and the Wilcoxon rank sum test were used for between-group comparisons of categorical and continuous data, respectively. A linear mixed-effect model analysis for repeated measurements within participants was used for continuous outcome measures (severity of superficial and deep sensations, and amplitude and velocity in the NCS). The fixed effects were the numbers of years the Toroku Medical Examination was administered, whereas the random effect was the patient. The statistical significance level was set at P = 0.05. Statistical analyses were performed using EZR (version 1.36, Saitama Medical Center, Jichi Medical University, Saitama, Japan) (Kanda 2013), which is a graphical user interface for R software (version 3.4.1, R Development Core Team; https://www.r-project.org/).

3. Results

3.1 Patient characteristics

The patient characteristics are summarized in Table 1. We enrolled 137 consecutive patients with chronic arsenic intoxication; 70 (51.1%) were male, and 91 (66.4%) had an occupational history that included work at the arsenic mine.

Table 1. Patient characteristics

Parameters	Total (n=137)
Men, n (%)	70 (51.1)
Previously worked at the arsenic mine, n (%)	91 (66.4)
Initial age of arsenic exposure, years	0 (0.0–16.0)

Age in 1962 when the mine closed	42 (34.0–51.0)
Survivors in 2014, n (%)	27 (19.7)
average age, years (survivors, n = 27)	81 (77.5–83.5)
average age of death, years (non-survivors, n = 110)	79 (70.3–85.0)

3.2 Longitudinal analysis of sensory dysfunction

The numbers of patients who met the inclusion criteria described in the Methods were 28 and 18 for the long-term follow-up of superficial and deep sensation, respectively. The patient characteristics are summarized in Table 2. The durations of follow-up were 30 years and 31 years for superficial and deep sensation, respectively. Both superficial and deep sensation worsened significantly during follow-up ($P = 0.04$ and $P < 0.01$, respectively).

Table 2. Patient characteristics and a mixed effect model: long-term follow-up of objective sensory dysfunction

Parameters	Objective sensory dysfunction	
	Superficial sensation (n = 28)	Deep sensation (n = 18)
Men, n (%)	11 (39.2)	6 (33.3)
Duration of arsenic exposure, years	38 (32.0–42.0)	29.5 (28.0–35.5)
Age in 1975, years	51 (44.8–55.0)	49 (44.3–53.0)
Survivors in 2014, n (%)	14 (50.0)	8 (44.4)
average age, years (survivors, n = 14)	84 (82.2–91.2)	82.5 (80.3–85.3)
average age of death, years (non-survivors, n = 14)	86 (77.8–88.0)	86.5 (76.3–88.0)
Follow-up duration, years	29 (27.8–34.0)	36 (31.3–40.0)
Mixed effect model		
Slope	6.16×10^{-5} *	2.06×10^{-4} **

* $P < 0.05$, ** $P < 0.01$

3.3 Nerve conduction study

For the NCS, between 30 and 44 patients were enrolled in each test according to the inclusion criteria. Results of the 10-year follow-up are shown in the Figure 1 (upper extremities) and Figure 2 (lower extremities). In the upper extremities, the compound muscle action potential (cMAP) of motor nerves and the nerve conduction velocity (NCV) of sensory nerves worsened significantly during the follow-up period ($P < 0.01$ and $P < 0.01$, respectively); in the lower extremities, the cMAP and NCV of the motor nerves worsened significantly ($P < 0.01$ and $P = 0.02$, respectively). The NCV of the sensory nerves in the lower extremities improved significantly during follow-up ($P < 0.01$).

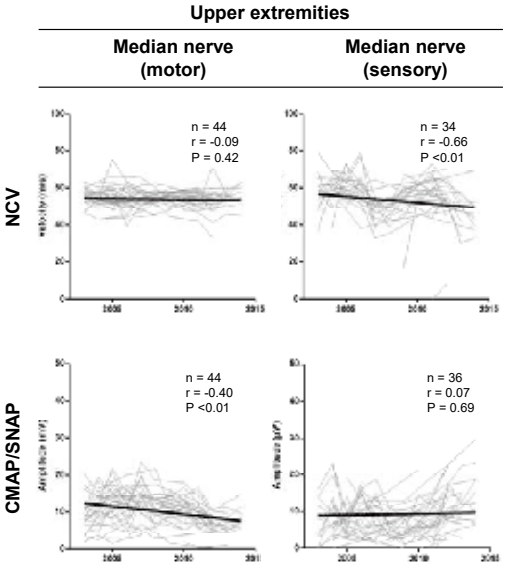

Fig 1. NCS in upper extremities

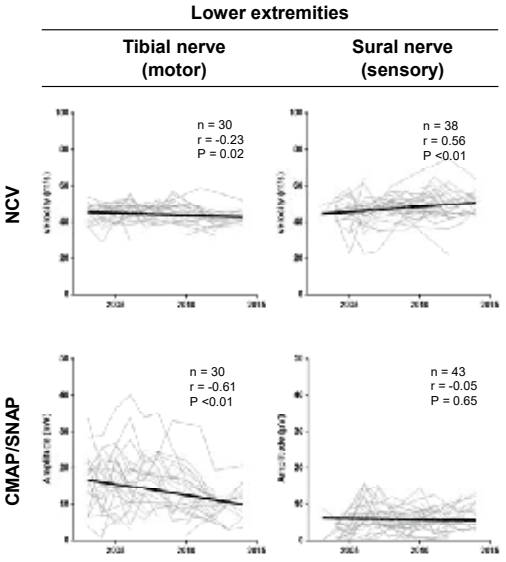

Fig 2. NCS in lower extremities

4. Discussion

Neurological examination and NCS showed that sensory dysfunction in patients with chronic arsenic intoxication worsened over the 40-year follow-up, a period that was long after the last exposure, although the nerve conduction

velocity of the sural nerve gradually improved. With increased age, even people with no comorbidities demonstrate decreased vibration sense in the toes and ankle joints after age 70 (Potvin et al. 1980), as well as reduced superficial sensation (Guergova and Dufour 2011) and impaired NCS (Rivner et al. 2001). In the NCS of patients with chronic arsenic intoxication, Supapong et al. (2004) found no significant difference compared with healthy controls, while other studies demonstrated significantly worse peripheral neuropathy in those exposed to arsenic (Feldman et al. 1979; Lagerkvist and Zetterlund 1994; Mukherjee et al. 2003). Therefore, the impaired sensory function observed in our study was not definitively due to chronic arsenic intoxication, but may rather have been age related.

Two different methodologies revealed a discrepancy in terms of lower limb sensation: NCS of the sural nerve improved, but sensory function evaluated by neurological examination worsened. We speculated that the improvement of nerve function on NCS was due to the fact that arsenic neuropathy is a length-dependent polyneuropathy (Rodriguez et al. 2003) that initially strongly affected the lower limbs; after cessation of arsenic exposure, severely injured sural nerves may have improved more than the aging-related worsening. In addition to the large fiber peripheral neuropathy, we hypothesized three possible causes of worsened sensation that would be unrelated to NCS findings: central nervous dysfunction, small fiber neuropathy, and skin disturbance. We previously revealed that patients in Toroku had prolonged central sensory conduction times compared with age-matched healthy subjects (Mochizuki et al. 2016). Small fiber neuropathy leading to pain and paresthesia was also reported to develop in patients with chronic arsenic intoxication (Sinczuk-Walczak et al. 2010; Sinczuk-Walczak et al. 2014). Indeed, pathological findings of the sural nerves of patients in Toroku showed reductions of both small myelinated fibers and unmyelinated fibers (Kawasaki et al. 2002). Moreover, in addition to skin aging, which is one cause of deterioration of superficial sensation in older adults (Guergova and Dufour 2011), chronic arsenic intoxication causes skin disturbance that may contribute to impairment of the intraepidermal nerve fibers as small fiber neuropathy. Taken together, the above factors would result in worsened sensation on neurological examination.

We have a following study limitation: a considerable part of patients with severe arsenic intoxication were not enrolled because a part of such patients died before 1962. Thus, some results in this study were less severe than they might have been if patients in more serious condition had been included.

In conclusion, sensory dysfunction of patients with chronic arsenic exposure had continued to gradually worsen over time even 40 years after exposure cessation. This is the first study to demonstrate the longitudinal sequelae of chronic arsenic intoxication long after exposure cessation. Our study will be helpful for assessing the prognosis of patients worldwide who still suffer from chronic arsenic intoxication.

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