Journal of the Neurological Sciences 361 (2016) 39–42

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Prolonged central sensory conduction time in patients with chronic arsenic exposure

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ARTICLE INFO

Article history:
Received 28 September 2015
Received in revised form 7 December 2015
Accepted 10 December 2015
Available online 12 December 2015

Keywords:
Arsenic exposure
Somatosensory evoked potential
Central sensory conduction time
Toxicity
Nervous system

ABSTRACT

Background: Many patients from Toroku, Japan, who have chronic arsenic exposure demonstrate whole-body sensory disturbance that is slightly more pronounced in the extremities. Although previous research in this population showed a mild peripheral neuropathy, it is unknown whether these patients have central nervous system impairment. To investigate the lesion sites underlying sensory disturbance related to chronic arsenic poisoning, we analyzed somatosensory evoked potentials (SEP).

Methods: Clinical features, nerve conduction study results, and median and/or tibial SEP were analyzed in patients with chronic arsenic exposure (total, 13 patients; median & tibial, 4; median, 5; tibial, 4) retrospectively. The SEP findings in patients were compared with those in normal controls.

Results: The median SEP results indicated a conduction delay between the proximal brachial plexus and the primary sensory cortex, and tibial SEP findings indicated a delay between the dorsal gray matter of the lumbosacral cord and the primary sensory cortex.

Conclusion: This is the first study to identify an impairment of the central somatosensory pathway in patients with chronic arsenic exposure. Sensory disturbance in these patients is related not only to peripheral neuropathy but also to impairment of the central nervous system.

1. Introduction

Toroku is a small village in a narrow valley in Miyazaki prefecture, Japan, and residents' houses are dotted along Toroku River. In the mid-twentieth century, arsenic was intermittently mined and refined at the Toroku mine; the roasters used at the mine's refinery were primitive, lacking dust-collecting systems. Therefore, enormous amounts of effluent gases containing arsenic trioxide leaked from the roasters and intermittently covered the entire Toroku valley between 1920 and 1962 [1,2]. About 280 residents were exposed to arsenic via food, water, air, and skin. Although arsenic concentrations in the environment were not measured during the mine's operation (1920–1962), they were investigated by Miyazaki prefecture in 1972 [1]. The dust from ceiling boards of residences near the mine revealed extremely high arsenic content (200–8000 mg/kg). The average arsenic concentrations in neighboring soil and in water percolating from the slag were 2760 mg/kg and 180 mg/L, respectively. The mean arsenic concentration in the hair of Toroku district residents (N = 29) was 1.52 mg/kg [1,3]. No arsenic air pollution occurred after 1962, but since many residents were still drinking the water from the polluted Toroku River, arsenic exposure continued long after 1962.

Some of the exposed individuals developed symptoms of chronic arsenic poisoning. Many whose poisoning was severe experienced serious respiratory, cardiovascular and skin diseases, and a large number died prior to 1962 [1]. However, more than 40 patients are still alive in 2015. Although about 50 years have passed since the mine was last operated, many patients still suffer from superficial and deep whole-body sensory disturbances of varying severity. These sensory disturbances were identified in the 1980s and most of them did not change markedly thereafter. A previous study [4] reported only mild axonal degeneration of peripheral nerves based on nerve conduction studies and sural nerve biopsies, and the authors speculated that arsenic exposure affected not only peripheral nerves but also other sensory pathways. Sensory disturbance due to peripheral neuropathy usually shows a glove-and-stocking type distribution. Most patients with sensory disturbance due to chronic arsenic exposure, however, show a whole-body sensory disturbance that is slightly more pronounced in the extremities. Sensory disturbance of the face or trunk might be a symptom of central nervous system impairment. In this study we investigated the somatosensory

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http://dx.doi.org/10.1016/j.jns.2015.12.020

pathway using median and tibial nerve somatosensory evoked potentials (SEP) in patients with chronic arsenic exposure.

2. Subjects and methods

This was a retrospective study.

2.1. Subjects

2.1.1. Patients with chronic arsenic exposure

All patients with chronic arsenic exposure underwent annual Toroku Medical Examinations (TME) from 1974 to the present. Prior to 1962 all patients lived within 1000 m of the mine roaster and had begun exhibiting skin findings (pigmentation or keratosis) typical of arsenic poisoning.

In 2012 and 2013, total 36 patients with chronic arsenic exposure underwent annual TME including neurological examinations. Based on the their medical records and neurological findings, 17 patients were excluded from this study because of diabetes mellitus, alcoholism, cervical or lumbar spondylosis, brain or spinal infarction, or other neurological disorders and two were excluded because of having cardiac pacemaker or the history of gastrectomy. In the remained 17 patients, 12 patients presented symmetrical sensory disturbances and were proposed to receive nerve conduction study and median SEP. Nine of them agreed to receive the additional physiological examinations. As same way, in 2014 and 2015, total 35 patients underwent annual TME and 17 of them were excluded because of their neurological disorders. Eleven out of the remained 18 patients presented symmetrical sensory disturbances and nine of them received nerve conduction study and tibial SEP. Four of the nine patients overlapped with the patients who underwent evaluation of median SEP. We analyzed these data retrospectively to investigate the sites of the lesions causing these patients' sensory disturbances. The blood analyses that had been routinely carried out during annual TME showed no remarkable abnormalities: the complete blood count and the levels of albumin, total cholesterol, and cholinesterase were all within normal ranges, and all patients were negative for syphilis.

2.1.2. Evaluation of sensory impairment

We evaluated sensory disturbances using 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. We qualitatively categorized sensory disturbances using five grades, as follows: '–' normal (normal sensation), '±' slight (slightly impaired), '+' mild (impaired, with greater than half of normal function), '++' moderate (impaired, with less than half of normal function), and '+++' severe (sensation almost disappeared). At least two neurologists blind to SEP results evaluated the sensory impairment of the bilateral forearms and legs using these tools and qualitatively determined the severity.

2.1.3. Exclusion by nerve conduction study

Nerve conduction studies of the right median, tibial, and sural nerves were performed in all above selected patients (N = 14). Most patients showed normal studies, but one individual demonstrated abnormally low-amplitude sensory nerve action potentials of the right sural nerve (below 4 μV) and was excluded from this study. SEP data of the remaining 13 patients (AS group) were analyzed (total, 13 patients; median & tibial, 4; median, 5; tibial, 4).

2.1.4. Normal controls for SEP

To obtain normal control values for SEP parameters, we established a control group consisting of 19 healthy volunteers ranging in age from the 60s to 80s (NL group; 10 for median SEP and 9 for tibial SEP). Based on the results of past SEP studies [5,6] and our hypothetical estimation that central conduction time is delayed by 15% in the arsenic group, the minimum sample size is at least eight in each group. However, there is no evidence in past studies supporting this 15% delay, since there have been no SEP studies in patients with arsenic exposure. We therefore recruited normal healthy volunteers in numbers equal to or greater than the arsenic group for both tibial and median SEP, until each normal group was age- and height-matched with the respective arsenic group. Healthy volunteers did not exhibit any neurological disorders. Written informed consent was obtained from all healthy volunteers.

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

2.2. Somatosensory evoked potentials

Median and tibial SEP were recorded in nine and eight of the 13 patients, respectively. In the median SEP examination, the right median nerve was stimulated at the wrist with a repetition rate of 3 Hz. The onset latencies of N9 (recorded at the ipsilateral Erb's point (EPi) and referenced to the contralateral Erb's point (EPc); a component of the proximal brachial plexus) and N20 (C3' (2 cm posterior to the C3 placement on the International 10–20 System) — Fz; primary somatosensory cortex) were analyzed according to previous papers (Fig. 1) [5,7,8].

In the tibial SEP examination, the right tibial nerve was stimulated at the ankle with a repetition rate of 2 Hz. We analyzed the peak latencies of P15 (contralateral iliac crest (ICc) — ipsilateral greater trochanter (GTi); junctional potential of greater sciatic foramen) and N21 (the first lumbar spinous process (L1) — GTi; post-synaptic potential in the dorsal gray matter of the lumbosacral cord), as well as the onset latency of P38 (Cz' (2 cm posterior to Cz) — C3'; primary somatosensory cortex), in accordance with previous papers (Fig. 1) [6,7,9]. The stimulus strength was fixed at about 1.2 times the motor threshold. Potentials were amplified by filters set at 1 and 1500 Hz, and at least 500 responses were averaged. To ensure the reproducibility of our results, we recorded SEPs at least twice.

There is controversy over whether latency measurements should utilize the onsets or peaks of SEP components. Several investigators have stressed the importance of using the onsets of these components because they are more relevant to physiological parameters such as the spinal entry time and the cortical arrival time [10–12]. Furthermore, for median SEPs, the onsets of the components were more stable than the peaks [5,12]. For tibial SEPs, a past study [6] tried to establish standard values and recommended that investigators employ the latencies of the P15 peak, N21 peak, and P38 onset for two reasons. First, the onsets of small components were difficult to define, and second, the P38 onset indicates the cortical arrival time and would more accurately reflect true conduction time than the P38 peak. For the reasons described above, in this study we employed the onsets of N9 and N20 for median SEPs and the P15 peak, N21 peak, and P38 onset for tibial SEPs.

2.3. Data analysis

Differences in SEP parameters between AS and NL groups were evaluated using the Mann–Whitney U test. No correlation for multiple comparisons were not performed. The statistical significance level was set at $P = 0.05$. SPSS version 22 software was used for statistical analysis.

3. Results

3.1. Clinical features

The clinical features of patients with chronic arsenic exposure are summarized in Table 1. They were exposed to arsenic between the ages of 0 and 37 years, and the duration of exposure ranged from 8 to 37 years. Their neurological findings showed mainly sensory disturbances with only slight motor symptoms. Their sensory disturbances were distributed throughout the entire body, with a slightly greater