Journal of the Neurological Sciences 398 (2019) 2–3

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Letter to the Editor

Auditory brainstem response analysis for long-term central auditory function sequelae in patients with chronic arsenic intoxication: A cross-sectional study

ARTICLE INFO

Keywords:
Arsenic
Chronic arsenic intoxication
Auditory brainstem response
Ototoxicity

Dear Editor

Chronic arsenic intoxication, a major threat to worldwide public health, reportedly affects the peripheral nervous system and causes sensorimotor polyneuropathy [1]. Arsenic also impairs the central nervous system including the somatosensory and visual functions as detected with neurophysiological methods [2,3]. Regarding central auditory function, although previous studies revealed the ototoxicity of arsenic [4], only one study with auditory brainstem response (ABR) analysis has been conducted and showed no abnormalities in patients actively exposed to arsenic via contaminated water [5]. However, the long-term auditory sequelae after arsenic exposure cessation have never been evaluated.

In Japan, many residents of Toroku village in the Miyazaki prefecture had developed arsenicosis due to oral, dermal, and tracheal exposure to highly-concentrated arsenic from the arsenic mines from 1920 to 1962 [2,6]. The surviving residents have undergone annual medical examination (Toroku Medical Examination) for > 40 years since 1974, revealing auditory abnormalities including subjective symptoms and objective neurological-examination findings in a cumulative 90% and 50% of the residents, respectively [6].

Here, using the ABR method, we evaluated the long-term sequelae of the central auditory function in the Toroku residents with chronic arsenic intoxication after exposure cessation compared with age-matched controls.

1. Methods

This retrospective cross-sectional study included 18 patients who (1) had lived in Toroku village prior to 1962, (2) were diagnosed with chronic arsenic intoxication by a governmental medical committee, (3) underwent the Toroku Medical Examination in 2017 and/or 2018, and (4) had no organic ear abnormalities and no hearing-acuity lateralities as assessed by neurological examination. Sixteen age-matched healthy controls were also enrolled in this study, and the 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. The study was conducted in accordance with the Declaration of Helsinki.

ABR analysis was conducted using Neuropack MEB2200 (Nihon Kohden, Tokyo, Japan). The right ears were stimulated by 90-dB clicks at a 10-Hz rate, while a − 40-dB white masking noise was applied to the left ear. Potentials were amplified by filters set at 50 and 3000 Hz, and at least 1000 responses were averaged. Absolute wave latencies of the I, III, and V waves and interwave latencies of I-III, III-V, and I—V were analyzed (recorded at the right mastoid – Cz). To ensure replication of the results, ABRs were recorded at least twice.

2. Results

Table 1 summarizes the patient characteristics and the results of the ABR analysis. The median age of the arsenic-exposure group was 78 years and was not significantly different from that of the control group. Six patients (33%) in the arsenic-exposure group had subjective hearing symptoms. All patients in the arsenic-exposure group were born in Toroku village and exposed from birth to 1962 when the arsenic mines closed. The median duration of arsenic exposure was 20 years, and no patient had worked in the arsenic mines. In the ABR analysis, the absolute wave latencies of waves I, III, and V and the interwave latencies of I–III, III–V, and I—V were comparable between the two groups.

3. Discussion

Here, we demonstrated that the central and peripheral auditory functions measured with the ABR method were comparable between patients with chronic arsenic intoxication and age-matched normal controls. Meanwhile, the previous epidemiological study revealed that more than half of Toroku residents had subjective and objective hearing abnormalities [6]. We hypothesize that the reasons for this discrepancy were as follows: (1) the ABR method could not evaluate the central auditory cortex and (2) the click sounds used in the ABR method could not evaluate the portions of the cochlea that are likely affected by arsenic toxicity.

Abbreviations: ABR, auditory brainstem response; SEP, somatosensory evoked potential; VEP, visual evoked potential

https://doi.org/10.1016/j.jns.2019.01.010
Received 27 November 2018; Received in revised form 5 January 2019; Accepted 8 January 2019
Available online 08 January 2019
0022-510X/

Table 1
Patient characteristics, arsenic exposure history, and auditory brainstem responses.

Parameters	Exposed group (n = 18)	Control group (n = 16)	P value
Patient characteristics			
Age, year	78.0 (70.6–81.0)	77.5 (53.3–80.0)	0.15
Men, n	8 (44.4)	12 (75.0)	0.09
Subjective hearing symptoms	6 (33.3)	–	–
Arsenic exposure history			
Age at exposure onset, year	0 (0–0)	–	–
Exposure duration, year	20.0 (15.3–26.8)	–	–
Employed at the arsenic mine, n	0 (0)	–	–
Auditory brainstem response			
Absolute wave latencies, ms			
I	1.44 (1.40–1.52)	1.50 (1.41–1.59)	0.24
III	3.59 (3.54–3.76)	3.77 (3.66–3.90)	0.13
V	5.62 (5.54–5.71)	5.75 (5.67–5.84)	0.06
Interwave latencies, ms			
I–III	2.18 (2.09–2.33)	2.28 (2.16–2.35)	0.46
III–V	1.96 (1.87–2.04)	2.00 (1.88–2.06)	0.69
I–V	4.13 (4.09–4.22)	4.23 (4.16–4.30)	0.16

Categorical variables are shown as numbers (percentages) and continuous variables are shown as medians (25th–75th percentiles). Fisher's exact test and the Mann-Whitney U test were used for between-group comparisons of categorical and continuous data, respectively.

Previous electrophysiological studies evaluating central sensory systems in patients with chronic arsenic intoxication used somatosensory evoked potentials (SEPs) and visual evoked potentials (VEPs) and they showed dysfunctions in the central somatosensory and visual cortex, respectively [2,3]. The SEP and VEP electrical potentials are generated by the cerebral cortex, while those of ABRs are generated by the brainstem. ABR analysis, therefore, could not evaluate auditory-cortex function even if arsenic toxicity had affected it.

Both this study and a previous one [5], revealed that there were no wave I differences between patients and controls, suggesting that the peripheral auditory tract was unaffected. We speculate that the result is attributable to the selectivity of arsenic toxicity for the cochlear hair cells. An experimental study showed that arsenic first impaired the hair cells in the apical side of the cochlea, the portion of which transmits lower-frequency sounds [7]. Several clinical studies have also revealed that arsenic toxicity selectively affects lower-frequency transmission [8,9]. Meanwhile, the click sounds used in ABR analysis have a higher frequency (2000–4000 Hz), allowing ABR methods to assess only high-frequency sounds, while they fail to evaluate low-frequency (500–2000 Hz) sounds related to speech perception [10]. As a result, the ABR method used here might have been unable to determine whether the patients had peripheral auditory impairment even if wave I was normal.

There were several limitations to this study. First, relatively few patients with severe arsenic intoxication were enrolled because most had died before 2017. Second, we did not measure hearing function with pure tone audiometry; therefore, peripheral auditory function was not fully evaluated. Third, we cannot deny the possibility of spontaneous auditory-function recovery after exposure cessation in patients with chronic arsenic intoxication because this was a cross-sectional study and no previous studies have longitudinally evaluated arsenic ototoxicity.

In conclusion, the participants with chronic arsenic intoxication had age-appropriate hearing function 40 years after exposure cessation evaluated with ABR analysis. This is the first study to reveal the long-term sequelae of the central auditory system in chronic arsenic intoxication with the ABR method. The discrepancy between the subjective hearing symptoms and the normal ABR results remains unresolved; ABR may not be affected by chronic arsenic poisoning. Further investigation is needed to determine whether arsenic toxicity affects the auditory cortex due to the limitations of ABR analysis mentioned above.

Acknowledgements

The authors thank all participants, physicians, laboratory technicians, and officials of the Miyazaki prefecture who cooperated with the Toroku Medical Examinations.

Funding

This study was partly supported by JSPS KAKENHI Grant Number JP18K10052 (HM).

Declarations of interest

None

References

[1] K.S. Abdul, S.S. Jayasinghe, E.P. Chandana, C. Jayasumana, P.M. De Silva, Arsenic and human health effects: a review, Environ. Toxicol. Pharmacol. 40 (3) (2015) 828–846, https://doi.org/10.1016/j.etap.2015.09.016.
[2] H. Mochizuki, K. Yagi, K. Tsuruta, A. Taniguchi, N. Ishii, K. Shiomi, M. Nakazato, Prolonged central sensory conduction time in patients with chronic arsenic exposure, J. Neurol. Sci. 361 (2016) 39–42, https://doi.org/10.1016/j.jns.2015.12.020.
[3] H. Sinczuk-Walczak, M. Szymczak, T. Halatek, Effects of occupational exposure to arsenic on the nervous system: clinical and neurophysiological studies, Int. J. Occup. Med. Environ. Health 23 (4) (2010) 347–355, https://doi.org/10.2478/v10001-010-0034-3.
[4] G.G. Kesici, Arsenic ototoxicity, J. Otol. 11 (1) (2016) 13–17, https://doi.org/10.1016/j.joto.2016.03.001.
[5] S. Supapong, J. Sriratanabun, Brainstem auditory evoked potentials (BAEPs) study in chronic arsenic poisoning patients, J. Med. Assoc. Thail. 88 (Suppl. 4) (2005) S226–S230.
[6] N. Ishii, H. Mochizuki, Y. Ebihara, K. Shiomi, M. Nakazato, Clinical symptoms, neurological signs, and electrophysiological findings in surviving residents with probable arsenic exposure in Toroku, Japan, Arch. Environ. Contam. Toxicol. 75 (4) (2018) 521–529, https://doi.org/10.1007/s00244-018-0544-8.
[7] M. Anniko, Atoxyl-induced damage to the sensory cells in the organ of Corti in the Guinea pig cochlea, Virchows Arch. B Cell Pathol. 21 (4) (1976) 267–277.
[8] J.E. Saunders, B.G. Jastrzembski, J.C. Buckey, D. Enriquez, T.A. MacKenzie, M.R. Karagas, Hearing loss and heavy metal toxicity in a Nicaraguan mining community: audiological results and case reports, Audiol. Neurootol. 18 (2) (2013) 101–113, https://doi.org/10.1159/000345470.
[9] V. Bencko, K. Symon, Test of environmental exposure to arsenic and hearing changes in exposed children, Environ. Health Perspect. 19 (1977) 95–101, https://doi.org/10.1289/ehp.771995.
[10] M. Francois, E. Dehan, M. Carlevan, H. Dumont, Use of auditory steady-state responses in children and comparison with other electrophysiological and behavioral tests, Eur. Ann. Otorhinolaryngol. Head Neck Dis. 133 (5) (2016) 331–335, https://doi.org/10.1016/j.anorl.2016.07.008.

Nobuyuki Ishii[a,*], Hitoshi Mochizuki[a], Mitsunori Yamashita[b], Kazuhiro Yagi[b], Kazuataka Shiomi[a], Kazuhito Tsuruta[b], Masamitsu Nakazato[a]
[a] *Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, University of Miyazaki, Japan*
[b] *Brain and Nerve Center, Junwakai Memorial Hospital, Japan*
E-mail address: nobuyuki_ishii@med.miyazaki-u.ac.jp (N. Ishii).

[*] Corresponding author at: Division of Neurology, Respirology, Endocrinology and Metabolism, Department of Internal Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan.