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# Peripheral nerve injury in patients exposed to *n*-hexane: an analysis of eight cases

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Poisoning is often characterized by the acute onset, rapid progress, or specific manifestations of pathological symptoms, such as pulmonary fibrosis due to paraquat poisoning or high mortality arising from dinitrophenol intoxication (Jiang et al., 2016; Wang et al., 2017; Feng et al., 2018; Lu, 2018; Xu and Lu, 2019). Unlike general poisoning, however, the manifestation of *n*-hexane intoxication is subacute, and its clinical symptoms are dormant, and thus the provision of a timely and correct diagnosis is often difficult.

Haining, located in the Zhejiang Province of Southeast China, is famous for its leather industry. An adhesive glue containing *n*-hexane ($C_6H_{14}$) is widely applied in the production of leatherware; therefore *n*-hexane can be absorbed through skin contact and accumulate in the body. Thus, occupational *n*-hexane intoxication occasionally occurs where effective protective measures are lacking. *n*-Hexane poisoning can result in the damage of multiple organs including the eyes, the heart, and the liver. Furthermore, extensive exposure to *n*-hexane also causes motor and sensory neurological dysfunction, which presents as hypodynamia and the numbness of distal extremities (Wang et al., 2014).

In this paper, we report a case series of eight patients from similar leather factories in Haining, who were admitted to our emergency department (ED) (the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China) and diagnosed with *n*-hexane poisoning between March and May 2018. All patients were confirmed to have a similar occupation and a clear history of *n*-hexane exposure. One of the authors of the present study personally oversaw the treatment of all eight patients. Patient information, such as demography data, clinical symptoms, clinical outcomes, as well as physical and auxiliary examinations, was extracted from hospital records. Further data including the course of disease, time to onset and peak of symptoms, and treatment details were also obtained and further analyzed. Our retrospective study proposal was approved by the Ethical Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (No. 20191310).

On March 1, 2018, a 50-year-old female admitted to our hospital complained of progressive numbness in the upper extremities and hypodynamia in the lower extremities one month after starting work in a leather factory. Thereafter, a young male (33 years old) visited the ED poisoning treatment and control center with similar symptoms. Both worked in a similar environment in leather factories located in Haining, and thus their cases were considered as occupational poisoning. Other workers in the same factories were subsequently asked to have a medical examination. In the end, six further workers presented to different medical clinics with similar symptoms were identified in the next two months (Table 1). The time period they had spent working in the industry ranged from two months to two years. In order to aid prompt diagnosis, the adhesive material used in the workplaces of these patients was further investigated and found to contain excess *n*-hexane. The latest data supported by the Public Health England (2016) determine the upper explosive

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limit of hexane as ⩽7.5% (volume fraction), and its concentration limit of organ damage through prolonged or repeated exposure as ⩽5%. However, the organic solvents used in the adhesives in question contained over 18% of *n*-hexane; also, no workers involved in these cases had any effective personal protective equipment fitted.

Most of the eight patients presented progressive weakness and numbness in the limbs, while no other type of discomfort was reported. The details of general patient conditions are shown in Table 1. Interestingly, all patients had a history of treatment at a local hospital, with a fairly high rate (87.5%) of misdiagnosis. Patients had misdiagnoses of peripheral neuropathy (3/8), peripheral neuritis (2/8), acute inflammatory demyelinating polyneuropathy (1/8), and Guillain-Barré syndrome (1/8). Their vital signs were stable upon arrival at the ED, and their muscle strength was graded as between 1 and 5 on a scale of 1−5 in the arms and legs by physical examination. In addition, different degrees of impairment of superficial sensation and tendinous reflex were found bilaterally in their upper or lower extremities.

Due to the peripheral neurotoxicity of *n*-hexane, the electromyogram (EMG) is necessary for proper diagnosis. Subsequent EMG results suggested that all patients showed varying degrees of neurological damage (Fig. 1). With respect to motor neuron conduction velocity (MNCV), the conduction velocity of the unilateral medial and ulnar nerve motor neurons was decreased in seven patients, with all such reductions on the right side. The remaining patient presented bilateral median nerve and ulnar nerve injury. In addition, the reduction of motor nerve conduction velocities of the bilateral radial and phrenic nerves was observed in all patients. In terms of sensory nerve conduction velocity (SNCV), different degrees of SNCV reduction were found in all patients. It is interesting to note that most patients presented a unilateral SNCV reduction in the same manner as MNCV.

All patients were hospitalized and subjected to a rehabilitation program. Since no known antidote for chronic *n*-hexane poisoning exists, patients were given symptomatic and supportive care. Neurotrophic drugs were necessary in most cases: 500 μg mecobalamin was intramuscularly administered daily, followed by an infusion of 100 mg vitamin B1. Patients were given 20−40 mg dexamethasone as an initial dose daily during the first week, and this dose was halved for two further weeks of drug treatment. Moreover, occupational therapy and strengthening exercises, including bedside exercise for mobility, were carried out. Six patients accepted acupuncture and showed improvements, as evidenced by clinical findings.

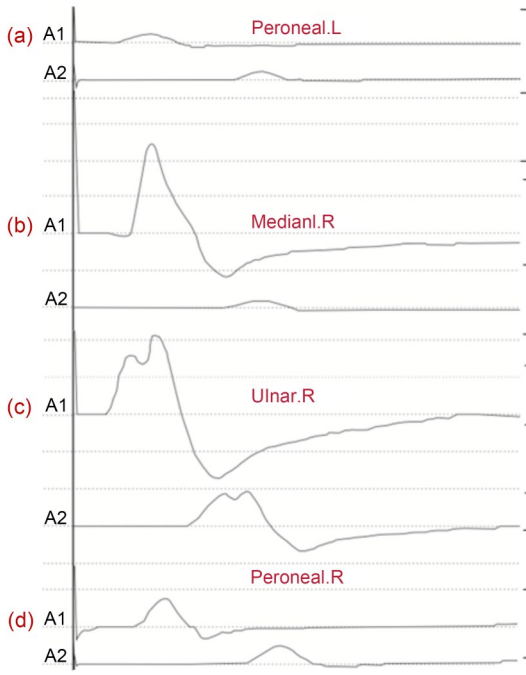
The patient rehabilitation program lasted for six to eight months. The muscle strength of all patients was effectively restored in the upper and lower extremities, while half of the patients still exhibited lowered tendon reflex. Although the shallow sensation had improved since admission, five patients did not fully recover in this aspect.

The neurofilamentous swelling of large myelinated axons in the peripheral nervous system (PNS) and the central nervous system (CNS) was identified as a morphological feature of *n*-hexane poisoning, which had been the focus of mechanistic disease research in the past 30 years (LoPachin and DeCaprio, 2004). Though the mechanism of neurotoxicity of *n*-hexane has not been elucidated completely, it has been demonstrated that neuron injury can be induced by the active γ-diketone metabolite, 2,5-hexanedione (2,5-HD) (Pastore et al., 2002). As reported previously, its potential mechanisms include neuronal energy metabolism and axonal transport disorders (Pan et al., 2017). Findings showed that 2,5-HD

**Table 1 Patient demographics and clinical features upon admission**

| Patient ID | Age (year) | Sex | Clinical features upon admission | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *T* (°C) | First diagnosis | Contact time (month) | Poisoning time (month) | Adynamia | | Numbness | |
| | | | | | | | Upper limbs | Lower limbs | Upper limbs | lower limbs |
| Case 1 | 50 | F | 37.1 | Peripheral neuropathy | 6 | 1 | | Y | Y | |
| Case 2 | 33 | M | 37.0 | Peripheral neuropathy | 6 | 1 | Y | Y | Y | Y |
| Case 3 | 41 | M | 36.8 | Peripheral neuritis | 6 | 1 | Y | Y | Y | Y |
| Case 4 | 35 | F | 36.5 | Peripheral neuritis | 6 | 2 | Y | Y | Y | Y |
| Case 5 | 28 | F | 37.0 | Unknown | 6 | 0.7 | | Y | Y | |
| Case 6 | 45 | F | 37.6 | Acute inflammatory demyelinating polyneuropathy | 2 | 2 | Y | Y | Y | Y |
| Case 7 | 44 | M | 36.8 | Guillain-Barré syndrome | 6 | 2 | Y | Y | Y | Y |
| Case 8 | 51 | M | 37.3 | Peripheral neuropathy | 24 | 1 | | | Y | Y |

ID: identification; F: female; M: male; *T*: temperature; Y: yes.




| Stimulate site | Lat (ms) | Dur (ms) | Amp (mV) | Area (mV·ms) | CV (m/s) |
|---|---|---|---|---|---|
| A1: Fibula (head) | 4.8 | 6.8 | 1.1 | 4.3 | 26.7 |
| A2: Popliteal fossa | 17.5 | 6.7 | 0.8 | 3.1 | |

| Stimulate site | Lat (ms) | Dur (ms) | Amp (mV) | Area (mV·ms) | CV (m/s) |
|---|---|---|---|---|---|
| A1: Wrist | 5.8 | 7.5 | 4.1 | 14.6 | 20.7 |
| A2: Below elbow | 16.6 | | 0.4 | | |

| Stimulate site | Lat (ms) | Dur (ms) | Amp (mV) | Area (mV·ms) | CV (m/s) |
|---|---|---|---|---|---|
| A1: Wrist | 3.7 | 7.9 | 3.5 | 15.9 | 30.6 |
| A2: Below elbow | 12.5 | 8.7 | 1.5 | 7.4 | |

| Stimulate site | Lat (ms) | Dur (ms) | Amp (mV) | Area (mV·ms) | CV (m/s) |
|---|---|---|---|---|---|
| A1: Fibula (head) | 4.2 | 7.1 | 1.4 | 5.2 | 28.6 |
| A2: Popliteal fossa | 16.6 | 7.9 | 0.6 | 3.0 | |

**Fig. 1 Electromyogram of one of the *n*-hexane poisoning patients in our cases. (a) Left peroneal nerve; (b) Right ulnar nerve; (c) Right medium nerve; (d) Right peroneal nerve. The recording site for upper limbs was the abductor pollicis brevis, whereas the recording site for lower limbs was the extensor digitorum brevis. L: left; R: right; Lat: latency; Dur: duration; Amp: amplitude; Area: conduction area; CV: conduction velocity.**

selectively interacts with the lysine residues of neurofilament to form pyrrole adducts that can be further oxidized, which subsequently accumulate and lead to axonal swelling (DeCaprio et al., 2009). What is more, 2,5-HD was demonstrated to inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH), the key enzyme in the glucose metabolism pathway, and subsequently reduce the production of axon energy, which might deteriorate transport dysfunction (LoPachin et al., 2002). However, recent evidence for animals indicates that axonal atrophy is a prevalent effect occurring during the early stages of exposure to a wide range of daily dose, while axonal swelling only exists in the low-dose group (LoPachin et al., 2003; Pannangrong et al., 2019). Also, 2,5-HD inhibits the expression of neurofilament proteins to reduce the axonal neurofilament content. Other studies found no obvious decline in the neurofilament content of the sensory ganglion in the low-dose group, while a 20% reduction was shown in the medium-dose group (Opanashuk et al., 2001). Thus, we assume that motor neurons are more vulnerable to 2,5-HD than sensory neurons, which is consistent with the EMG findings in our cases.

Patients with *n*-hexane poisoning are often misdiagnosed as general neuropathies at first assessment. According to current guidelines, the diagnosis of *n*-hexane intoxication must meet the following criteria: (1) a clear history of *n*-hexane exposure; (2) clinical manifestations of multiple peripheral neuropathy; (3) EMG showing neurological damage; (4) increased 2,5-HD content in the urine; and, (5) exclusion of other peripheral neurological diseases (Xia and Yan, 2018). It is of high importance to identify the occupational history of patients for the prompt diagnosis of *n*-hexane poisoning. The 2,5-HD content in urine also has a significant contribution to accurate diagnosis, as it can indicate whether the patient has been exposed to *n*-hexane during the past month; however, no clear correlation was established between its concentration and the severity of poisoning (Prieto et al., 2003). Unfortunately, this method of detection has not been popularized in most hospitals of China. A further important method of diagnosis of *n*-hexane poisoning is electromyography, which presents a decrease in the amplitude of combined nerve and muscle action potential, an increase in distal latency values, and the slowing down of transmission in EMG (Pastore et al., 2002; Pan et al., 2017).

In our case report, the symptoms of adynamia and limb numbness had been significantly improved by

the time patients were discharged. The physical examination showed that all patients had a well-restored motor function. However, only half of the patients had recovered tendon reflexes, which is consistent with a previous case report (Sendur et al., 2009). Moreover, we found that certain patients had developed sensory nerve dysfunction at the same time, and the recovery of sensory nerves lasted much longer than expected. A further significant finding emerging from this study is that physical examination showed symmetric sensorimotor deficits of the distal extremities, while EMG results revealed that the nerve injury was worse on the right side than on the left side, which was inconsistent with the clinical signs.

Based on the findings of our case series study, we suggest that when doctors encounter patients with clinical manifestations of motor and sensory dysfunction, they should also consider the possibility of *n*-hexane poisoning besides diseases of the nervous system. Also, the occupation of patients is non-negligible information for correct diagnosis.

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## Author contributions

Xiaping ZHANG performed the research and data analysis, and wrote and edited the manuscript. Yaling TONG performed data analysis. Yuanqiang LU contributed to the study design, data analysis, and writing and editing of the manuscript. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

## Compliance with ethics guidelines

Xiaping ZHANG, Yaling TONG, and Yuanqiang LU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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