Neuropathy caused by addictive inhalation of n-hexane in glue sniffers

Neuropathie secondaire à l’inhalation du n-hexane chez les sniffeurs de colle

N-hexane, an aliphatic hydrocarbon that is an isomer of hexane, is a common component in lacquers, glues and cleaning agents in different industries [1]. It was identified as a peripheral neurotoxin in 1964 [2]. Recently, inhalation of glue vapors has become popular among teenagers in Morocco as an addiction.

In clinical terms, exposed persons usually show progressive distal numbness in the limbs [3]. Weakness develops in the legs, then the arms, and tends to affect distal muscles the most [4]. Acute worsening may generate the differential diagnosis of Guillain Barré syndrome (GBS) [5].

Many forms of n-hexane neuropathy resulting from industrial exposure have been described [6], but few reports on glue sniffing as a cause of peripheral nerve involvement have been reported from Japan [7,8] and the United States [9,10]. The authors report 3 cases with acute or sub-acute neuropathy caused by addictive inhalation of n-Hexane. Considering the clinical manifestations: high levels of n-hexane in glue used in inhalation, appropriate temporality of the relationship between exposure and disease, and exclusion of other causes, our patient's polyneuropathy was closely associated with exposure to n-hexane.

Observations

Observation 1

A 25-year-old male patient, whose past history was significant for glue sniffing for many years (6 years), chronic smoking and occasional alcohol consumption. Our patient complained of progressive numbness and progressive weakness (table 1).

Six weeks earlier, he had developed weakness first in the right lower limb, then the left lower limb. The weakness progressed extending to the upper 2 limbs, followed by a decrease in visual acuity in the left eye, without sensory disturbances, respiratory distress, swallowing disorders or bowel and bladder involvement.

Neurological examination showed a proximal-distal weakness predominantly in the lower limb. Deep tendon reflexes were absent all over and plantar responses were flexor. Eye examination showed an isolated decrease in visual acuity in the left eye, fundus exam and visual champs were normal and general physical examination was normal.

Electrophysiologic evaluation was suggestive of a motor demyelinating and axonal polyneuropathy, with an absence of the motor potentials in the lower limbs and a prolongation of distal latency of the median and ulnar nerves, without fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for CIDP (table 1).

A brain MRI was performed and was normal. Laboratory evaluation was normal and included a complete blood count, electrolytes, liver function tests, a sedimentation rate and serum protein electrophoresis, cerebral spinal fluid study was normal and TPHA-VDRL and HIV tests were negative (table 1).

After his hospitalization, our patient received a supplementation of vitamin B complex (B1-B6) as a medication with daily sessions of motor rehabilitation. Clinical course showed an improvement with progressive recovery after weaning.

Observation 2

A 24-year-old male patient with a 3-year history of glue sniffing was admitted to neurological emergencies for a weakness of upper and lower extremities evolving 2 weeks earlier (table 1). Onset was symmetrical, slowly progressive, and present in both feet to begin with and gradually ascended, and then he noticed difficulty in walking and climbing. He also stated a feeling of numbness and some weakness in his upper limbs, and over the next week, he became chair bound. There was a 5-kg weight loss with associated anorexia.

The neurological examination showed a proximal-distal weakness predominantly in the lower limb. Deep tendon reflexes were absent all over and plantar responses were flexor.

Electroneuromyography showed an axonal and demyelinating polyradiculoneuropathy with Partial motor conduction block of the median nerve between the wrist and the elbow (figure 1) and denervation signs in the lower limbs, without fulfilling the EFNS/PNS criteria for CIDP (table 1).

Laboratory evaluation was normal and included a complete blood count, electrolytes, liver function tests, a sedimentation rate and serum protein electrophoresis; cerebral spinal fluid study was normal and TPHA-VDRL and HIV tests were negative.

The patient received a supplementation of vitamins B1 and B6 and the same rehabilitation protocol as in the first case was applied to him. The clinical course showed a partial improvement with progressive recovery after weaning.
Table I  
**Clinical features and laboratory investigations**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Addiction duration</th>
<th>Symptom onset</th>
<th>Limb strength:</th>
<th>Neurological examination findings</th>
<th>Laboratory investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>6 years</td>
<td>6 weeks</td>
<td>P 3/5, D 3/5-</td>
<td>absent in upper and lower extremities</td>
<td>Normal</td>
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<td></td>
<td></td>
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<td></td>
<td>U 4/5, D 4/5</td>
<td>Sensory: normal</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cranial nerves: examination: normal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>M</td>
<td>3 years</td>
<td>2 weeks</td>
<td>P 2/5, D 2/5</td>
<td>absent in upper and lower extremities</td>
<td>Normal</td>
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<td>Sensory: normal</td>
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<td>Cranial nerves: examination: normal</td>
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<tr>
<td>3</td>
<td>27</td>
<td>M</td>
<td>10 years</td>
<td>4 weeks</td>
<td>P 1/5, D 1/5.</td>
<td>absent in upper and lower extremities</td>
<td>Normal</td>
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<td></td>
<td></td>
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<td>Sensory: glove and stocking type sensory impairment</td>
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<td>Cranial nerves: examination: bilateral facial paresis</td>
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</tr>
</tbody>
</table>

DTR: deep tendon reflexes.  
*MRC scale: P = proximal; D = distal.*

Table II  
**Electrophysiological features in our patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Motor nerve (DL/A/C)</th>
<th>Sensory nerve (DL/A/C)</th>
<th>F response</th>
<th>Focal conduction block</th>
<th>Needle EMG</th>
<th>EMG conclusion</th>
</tr>
</thead>
</table>
| 1       | Median: 4.2 ms, 0.8 mV, 32.3 m/s  
Ulnar: 4.4 ms, 1 mV, 36.9 m/s  
Peroneal: not obtained  
Tibial: not obtained | Median: normal  
Ulnar: normal  
Sural: 3.2 ms, 5 μv, 35 m/s | Median: 38 ms  
Ulnar: 40.5 ms  
Peroneal: not obtained  
Tibial: not obtained | No Conduction block | Polyphasic MUP Recruitment + Denervation + | Mixed demyelinating and axonal polyradiculoneuropathy in the lower extremities |
| 2       | Median: 9.3 ms, 4 mV, 22.8 m/s  
Ulnar: 10.5 ms, 4.2 mV, 26.2 m/s  
Peroneal: 9.6 ms, 0.1 mV, 18 m/s  
Tibial: 15.6 ms, 0.2 mV, 21 m/s | Median: 2.9 ms, 11 μv, 40.4 m/s  
Ulnar: 2.4 ms, 7.7 μv, 45.4 m/s  
Sural: 4.8 ms, 0.5 μv, 32.4 m/s | Median: 35.5 ms  
Ulnar: 31.1 ms  
Peroneal: not obtained  
Tibial: not obtained | Conduction block (upper limbs) | Polyphasic and wide MUP Denervation ++ Recruitment+ | Sensory-motor mixed (axonal and demyelinating) polynephropathy |
| 3       | Median: 6.8 ms, 0.6 mV, 36 m/s  
Ulnar: Not obtained  
Peroneal: Not obtained  
Tibial: Not obtained | Median: not obtained  
Ulnar: not obtained  
Sural: not obtained | Median: not obtained  
Ulnar: not obtained  
Peroneal: not obtained  
Tibial: not obtained | No Conduction block | Polyphasic and wide MUP Denervation ++ Recruitment+ | Axonal and demyelinating sensorimotor polyradiculoneuropathy |

*The average right limb/left limb.*

Observation 3  
A 27-year-old male patient was referred to our department from another institution. He suffered from weakness in his legs and instability to walk for the previous month. In his medical history, chronic alcoholism and glue sniffing for the 10 previous years were noted (table I).

The initial complaint started with difficulty in climbing stairs, then weakness of the upper limbs had been added within 2 weeks. There was a bladder involvement described as a urinary frequency. Moreover, a weight loss was noticed by the patient. Neurological examination showed a proximal-distal weakness predominantly in the lower limb. Deep tendon reflexes were
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![Graph of electromyography findings](image)

**Figure 1**
Median motor conduction study findings for patient 2. Conduction block is present between the wrist (upper trace: action potential amplitude = 4.5 mV) and elbow (lower trace: action potential amplitude = 1 mV)

In Morocco, inhalation of glue vapors is popular among teenagers as an addiction. This could be explained by several reasons: its low cost, availability and ease of use. The vast majority of consumers are boys: this explains that the 3 cases we have presented are male.

The majority of cases of n-hexane neuropathies reported in the literature are due to industrial exposure [2,3,14]. Addictive forms of n-hexane neuropathy have been described less: some cases from Japan [7,8], The United States [9,10] and Saudi Arabia [5] have been reported.

The neurotoxicity of n-hexane may occur in both the peripheral nervous system and central nervous system (CNS) [15]. Sensomotor polyneuropathy is the principal neurological manifestation in subacute or chronic exposure to n-hexane [1]. The onset is usually subacute or chronic, and the course is progressive with initial symptoms of numbness and burning sensation in the toes and fingers, followed by distal limb muscle weakness [1]. Muscle weakness often involves the extensor and flexor muscles of the forearms and legs. Moreover, the extensor muscles are usually affected more severely than the flexor muscles in the forearms and legs. Polyneuropathy related to n-hexane abuse has different features from the industrial n-hexane neuropathy: autonomic disturbances are often reported among glue sniffers as in one of our patients but not in industrial cases [16]. Moreover, the sensory and motor dysfunction caused by industrial toxicity usually develops insidiously which may be explained by the slow and low level of exposure [2]. Finally, in abuse cases, neurological manifestations are probably more severe than in chronic industrial exposure cases, because hexacarbon neurotoxicity is proportional to the intensity of exposure [3].

**Discussion**

The main metabolite of n-hexane in the organism is 2,5-hexadienone. This metabolite can cause peripheral neuropathy after excessive long-term exposure [2]. N-hexane neuropathy is known to affect the large diameter fibers, especially in the lower extremities [11]. Inhalation of volatile hydrocarbons including glue sniffing is widely prevalent [5,12]. An American published study reported that nearly 20% of adolescents in the USA have experimented its use [13].

Absent all over and plantar responses were flexor. Cranial Nerves examination showed a bilateral facial nerve palsy. Electroneuromyography showed an axonal and demyelinating sensitive motor polyradiculoneuropathy with denervation signs in the lower limbs (table II) with a significant prolongation of distal latencies of the median nerves, an absence of motor potentials in the lower limbs and ulnar nerves, without fulfilling the EFNS/PNS criteria for CIDP.

Electroneuromyography of facial nerves showed a prolongation of distal latencies with a decrease of amplitudes in both nerves. Urodynamic tests were not performed.

Laboratory evaluation was normal and included a complete blood count, electrolytes, liver function tests, a sedimentation rate and serum protein electrophoresis, cerebral spinal fluid study was normal and TPHA-VDRL and HIV tests were negative. The patient received a supplementation of vitamins B1 and B6 and motor rehabilitation. Clinical course showed a partial improvement with progressive recovery after weaning.
The onset in our three patients was subacute and reminiscent of subacute Guillain Barre syndrome, or vitamin B 12 deficiency. The cerebrospinal fluid findings, the normality of the dosage of vitamin B 12 helped us distinguish the two disorders. Thus, n-hexane neuropathy should be kept in mind in the diagnosis of a patient with neuropathy, especially if the patient is chronically exposed.

N-Hexane polyneuropathy is one of the few toxic neuropathies, which exhibit electrophysiological features of both demyelination and axonal loss [2]. However, n-hexane neuropathy is primarily an axonal neuropathy, most electrophysiological studies report demyelinating features such as the slowing of the nerve conduction velocity (NCV) (decrease > 40%) [3], focal conduction block (reduction > 50%) with temporal dispersion of compound muscle action potentials, and marked prolongation of distal latencies (> 50%), particularly in the lower extremities [1]. Another important feature is the denervation potentials namely sharp positive waves and fibrillations on needle EMG [4].

Electromyogram (EMG) changes of the distal lower limbs may occur earlier than those of the proximal limbs [17,18]. Although the electrophysiological findings are usually well correlated with the clinical findings, some electrophysiological findings have been reported even in subclinical cases. The EMG of our patients displayed conduction abnormalities in the lower extremities, more pronounced in the motor nerves. It could thus be deduced that motor involvement precedes sensory abnormalities in some cases.

The most common abnormalities were consistent with demyelination and included a prolongation of motor distal nerve latencies, a prolongation of minimal F wave latencies and a slowing of the nerve conduction velocities. Focal conduction blocks were noted in one patient (figure 7), in the other patients, their absence may be explained by the severe axonal impairment as was the case in patient 3. The results of our electrophysiological studies confirm the mixed axonal and demyelinating features that are consistent with the pathological findings in n-hexane intoxication. The EMG abnormalities in the present patients were more obvious in motor than in sensory conduction. This discrepancy was consistent with the fact that the motor deficit was more prominent than the sensory impairment.

The patients with a more severe deficit (cases 1 and 3) and with a longer duration on exposure had more marked abnormalities on the EMG.

The dosage of urinary level of 2.5- Hexadiene can confirm excessive exposure to n-hexane [19], but unfortunately, it was not available in our hospital and could not be performed in another center given the socioeconomic difficulties of our three patients.

To date, the patients with n-hexane intoxication have no known antidotes [1]. Weaning is the first step in therapeutic management. Supportive measures including physical and occupational therapy, supplementation in vitamin B complex (B1, B6) was suggested by our team and was given to all the patients. Stopping any exposure to the n-hexane is the first step to prevent neuropathy. Increased awareness of these neurotoxic substances among teenagers and glue sniffers may be helpful [1,12].

The clinical course in patients with n-hexane neuropathy tends to be biphasic: in a first period, the deterioration after discontinuation of exposure is described as "coasting". It is frequently seen and becomes maximal within two to three months, followed by a slow recovery of about 1 to 2 years after cessation of exposure to n-hexane [1,20].

Prognosis is often favorable: it depends on the severity, with excellent clinical outcome in most patients with sensory neuropathy [1]. Severely affected patients may develop sequelae of muscle wasting, foot drop, and spasticity.

N-hexane abuse causes severe subacute polyneuropathy. The electrophysiological features reflect the pathophysiology of this disorder. The most effective way to curtail inhalant abuse of n-hexane is prevention among adolescent abusers, which is of paramount importance.

Disclosure of interest: the authors declare that they have no competing interest.

References
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Received 9 June 2018
Accepted 4 April 2019
Available online: