

Can mustard gas induce late onset polyneuropathy?

MR. Azarpazhooh, MD.¹, A. Shoeibi, MD.², MR. Soroush, MD.³, S. Khateri, MD.⁴,
SJ. Mousavi, MD.⁵, and E. Modirian, MD.⁶

Neurology Department, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: Mustard gas, lethal in high doses, affects multiple organs such as skin, eye and respiratory system. We studied the development of late onset mustard-induced polyneuropathy among chemically wounded Iranian veterans.

Methods: In this descriptive study, 100 chemically wounded Iranian veterans with severe eye involvement were examined for any signs and symptoms of polyneuropathy by an internist. 20 patients were suspected to have neurological symptoms or signs. These patients were examined by a neurologist again. 13 showed abnormal neurological symptoms. Electrodiagnostic exams were performed for this group by another physician.

Results: 13 veterans had abnormal neurological exam results with prominent sensory signs and symptoms in almost all of them. Brisk deep tendon reflexes were found in 3 cases. Electrodiagnostic studies were compatible with axonal type distal sensory polyneuropathy in 6 subjects.

Conclusion: To the best of our knowledge, this is the first report of late onset polyneuropathy among chemically-wounded victims who were exposed to mustard gas. The pathophysiology of this form of neuropathy is still unknown. Unlike most toxic neuropathies, obvious clinical signs and symptoms appeared several years after exposure. No specific treatment for polyneuropathy due to chemical weapons exposure has been described to date.

Keywords: mustard gas, polyneuropathy, chemical weapon.

Introduction

Toxin-induced neuropathies, although uncommon, are important to identify because of potential reversibility. Numerous medications and toxins are implicated in relation with neuropathy, but objective proof lacks for many. Some established associations with neuropathy are less widely known while others are overestimated [1]. The early disturbances are mostly

symmetrical sensory symptoms and signs, often followed by symmetrical motor pareses. The best therapy is, of course, termination of exposure to the toxic substance [2].

Chemical-weapon induced neuropathy is one of the most unknown types of neuropathy. In the Iran-Iraq war, chemical weapons were used several times against Iranian soldiers and also citizens (UN document S/16433 Mar.26, 1984). In 1987, the United Nations' investigative envoy reported that Iran was subject to

1. **Corresponding author**, Assistant Professor of Neurology, Mashhad University of Medical Sciences, No.380, Sajad blvd, Mashhad, Iran. Email: r_azarpazhooh@yahoo.com, TEL: +9891531 56347, Fax: +98511 606 7489.

2. Resident of Neurology, Mashhad University of Medical Sciences.

3-6. General Practitioner, Janbazan Medical Engineering Research Center, Mashhad, Iran.

chemical weapons attacks. They visited 12000 chemical wounded soldiers, mostly affected by mustard gas (UN DocumentS/17911.Mar.12, 1986).

There were some reports in the "Iran Veterans Registry" of the obvious signs and symptoms of neuromuscular involvement after exposure. However, the exact rate of peripheral nerve disorders has not been studied. This might be related to the high mortality rate and also severe morbidity among chemically wounded veterans. Therefore, the symptoms and signs of neuropathies were overlooked in patients with severe eye, skin, and pulmonary disorders.

In this study we evaluated the prevalence of peripheral neuropathy among veterans with severe toxic eye involvement due to documented mustard gas exposure who had no obvious neurological complaints for several years after exposure.

Methods

In this descriptive study, 150 veterans from all parts of Iran with a history of severe eye involvement due to documented mustard gas exposure were thoroughly evaluated in Mashhad in 2007. Among them, 100 agreed to be examined for signs and symptoms of neuromuscular disorders. They participated in this study freely and willingly. General and neurological examinations were performed for all these patients by an internist. 32 patients with suspected neurological findings were referred to a neurologist. None of these patients had significant metabolic disorders.

Exclusion criteria were any of the following: 1) History of another disorder which could affect peripheral nerves such as metabolic disorders, or vitamin deficiency 2) History of medications which could affect peripheral nerves. 3) Positive family history for peripheral nerve disorders.

In the cases with obvious symptoms and signs of peripheral neuropathy, four-limb electromyography and nerve conduction studies

(sensory and motor) were performed by an expert physician who was also blind to clinical data.

Abnormal electrodiagnostic study was defined according to the standard definition of axonal, demyelinative and mixed neuropathy based on the changes in the velocity and amplitude as well as electromyography changes. In axonal injuries, there is initial loss of sensory nerve amplitude in a length-dependent fashion (i.e., first in the distal lower extremities) followed by loss of motor amplitudes (in sensorimotor axonopathy), with gradual spread of these abnormalities to the shorter nerve segments in the upper extremities. Because myelination is relatively preserved in primary axonal injury, distal latencies, conduction velocities, and late responses are not affected.

In a distal symmetric neuropathy, electromyography changes appear first in the distal muscles and may move proximally as the neuropathy worsens and the deficits ascend. In severe, acute processes, decreased motor unit recruitment and loss of a full interference pattern on voluntary contraction are the earliest indication of axon loss. With ongoing severe denervation, increased insertional activity and spontaneous activity appear, starting approximately 3 weeks after an acute injury, and may persist as long as the disease process remains active. Neurogenic motor unit action potentials do not appear for at least 2 to 3 months because of the time required for collateral reinnervation to become established [3].

Finally, neuropathy was diagnosed based on the definition of "the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine Rehabilitation", among which the combination of neuropathic symptoms, signs, and abnormal electrodiagnostic studies provide the most accurate diagnosis of distal symmetric polyneuropathy [4].

Results

From 100 veterans, with a documented histo-

Case	Age	Age at time of exposure	Interval between injury and neuropathic symptoms*	Severity of eye involvement*	Pulmonary involvement**	Skin involvement	Other diseases**
Case 1	44	22	19	Moderate	Mild	Negative	Negative
Case 2	51	27	23	Mild	Mild	Negative	Negative
Case 3	50	26	18	Severe	Moderate	Severe	Negative
Case 4	41	20	11	Severe	Negative	Moderate	Negative
Case 5	39	17	15	Moderate	Negative	Negative	Negative
Case 6	48	26	17	Moderate	Moderate	Mild	Negative
Case 7	61	39	16	Severe	Moderate	Moderate	Negative
Case 8	44	18	25	Mild	Severe	Negative	Negative
Case 9	36	14	12	Severe	Moderate	Mild	Negative
Case 10	38	16	17	Severe	Mild	Mild	Negative
Case 11	43	21	21	Severe	Negative	Moderate	Negative
Case 12	41	20	17	Severe	Severe	Negative	Negative
Case 13	48	26	17	Mild	Mild	Negative	Negative

* In years

** Based on panel of experts

Table 1. Demographic data of the patients.

ry of exposure to chemical mustard gas, during the Iran-Iraq conflict, 13 revealed clinical findings compatible with peripheral neuropathy. Table 1 shows the demographic data of these patients.

As shown in Table 2, the most important complaints were paresthesia and numbness. There were no symptoms and signs of autonomic dysfunctions. Muscle strength was normal and more interestingly deep tendon reflexes were normal or even brisk in some cases.

Peripheral nerve involvement was confirmed in 6 cases by electrodiagnostic studies (Table 3). Mild axonal sensory and motor polyneuropathy was the most frequent type of peripher-

al neuropathy.

Discussion

Toxic neuropathy is a complex, multifactorial disease which potentially affects individuals of all ages. The variety of agents producing neurotoxicity is wide, including inorganic toxins such as heavy metals; organic toxins such as organophosphates, acrylamide and its analogs, industrial solvents; therapeutic agents and plant alkaloids [5]. In this study we evaluated late-onset presentation of mustard neuropathy.

The two major threat classes of chemical weapons are mustard gas and nerve agents. Mustard gas, bis-(2-chloroethyl) sulfide (Chem-

Case	Chief complaints	Motor findings	Tendon reflexes	Sensory findings	Autonomic function	Other neurologic examinations
Case 1	Paresthesia	Normal	Decreased*	Stocking and gloves pattern**	Normal	Normal
Case 2	Paresthesia	Normal	Brisk	Stocking and gloves pattern**	Normal	Normal
Case 3	Paresthesia	Normal	Decreased*	Stocking and gloves pattern**	Normal	Normal
Case 4	Paresthesia	Normal	Decreased*	Stocking and gloves pattern**	Normal	Normal
Case 5	Paresthesia	Normal	Decreased	Stocking and gloves pattern**	Normal	Normal
Case 6	Paresthesia	Normal	Decreased*	Stocking and gloves pattern**	Normal	Normal
Case 7	Paresthesia	Normal	Normal	Stocking and gloves pattern**	Normal	Normal
Case 8	Paresthesia	Normal	Decreased	Stocking and gloves pattern**	Normal	Normal
Case 9	Paresthesia	Normal	Normal	Stocking and gloves pattern**	Normal	Normal
Case 10	Paresthesia	Normal	Brisk	Stocking and gloves pattern**	Normal	Normal
Case 11	Paresthesia	Normal	Brisk	Stocking and gloves pattern**	Normal	Normal
Case 12	Paresthesia	Normal	Decreased	Stocking and gloves pattern**	Normal	Normal
Case 13	Paresthesia	Normal	Normal	Stocking and gloves pattern**	Normal	Normal

* Achilles reflex decreased and other reflexes were normal

** Sensory loss for all modalities

Table 2. Neurological findings of the patients.

Case	Upper limbs		Lower limbs	
	Motor branches*	Sensory branches**	Motor branches***	Sensory branches****
Case 1	Normal	Axonal type neuropathy	Normal	Axonal type neuropathy
Case 2	Normal	Axonal type neuropathy§	Normal	Axonal type neuropathy
Case 3	Normal	Axonal type neuropathy	Normal	Axonal type neuropathy
Case 4	Normal	Axonal type neuropathy	Normal	Axonal type neuropathy
Case 5	Normal	Axonal type neuropathy	Normal	Axonal type neuropathy
Case 6	Normal	Axonal type neuropathy	Normal	Axonal type neuropathy
Case 7	Normal	Normal	Normal	Meralgia paresthetica
Case 8	Normal	Carpal tunnel syndrome	Normal	Normal
Case 9	Normal	Normal	Normal	Normal
Case 10	Normal	Normal	Normal	Normal
Case 11	Normal	Normal	Normal	Normal
Case 12	Normal	Normal	Normal	Normal
Case 13	Normal	Normal	Normal	Normal

*Median nerves, ulnar nerves

**Radial nerves, median nerves, ulnar nerves

***Deep peroneal nerves, tibial nerves

****Sural nerves, superficial peroneal nerves

§ More severe in upper limbs

Table 3. Electrodiagnostic findings of the patients.

ical Abstract Service No. 505-60-2), is also known as mustard, S-mustard, sulfur mustard, HS, HD, H, Kampstoffs, Lost, SLost, Schwefel-Lost, Y, Yellow Cross, and Yperite. At 25 degrees celsius, the vapor pressure, liquid density, and volatility of mustard are 0.11 mmHg, 1.27 g/mL, and 920 mg/m³, respectively. The nerve gases or nerve agents are all fluorine- or cyanide-containing organophosphates (OPs) similar to insecticides. They are the most potent of the known chemical agents, rapidly lethal, and are hazardous by any route of exposure. The nerve agent O-ethyl S-[2-(diisopropylamino) ethyl]methylphosphonothioate (VX) is estimated to be 103-104 times more potent than the most potent commercially available OP insecticides [6].

The first wartime use of mustard was by the Germans against the British at Ypres, Belgium, on 12 July 1917 [7]. Since World War I, mustard has been allegedly used by the following: Great Britain in the Middle East; the French in Morocco; Italy against Ethiopia in 1936; Japan against China in 1937; Poland against Germany in 1939; the Russians in Central Asia; Egypt against Yemen from 1963 to 1967; Iraq against Iran during the Iran-Iraq War, and Iraq against

the Kurds [8-12].

The most common symptoms in mustard-exposed victims are eye and skin lesions, with more severe cases having respiratory and gastrointestinal problems [13-15]. To the best of our knowledge, there is no report of late onset mustard-induced neuropathy in the literature. We found objective signs and electrodiagnostic findings of polyneuropathy among 13% and 6% of our patients, respectively. None of our patients had any complaints of neuromuscular disorders for several years after exposure, although this might be due to severe comorbid injuries. Ruling out metabolic and other toxic neuropathies and not having a positive family history of neuropathic disorders, we concluded that these neuropathies might be mustard-induced.

Most toxic peripheral neuropathies are sensory-motor with predominant sensory symptoms [16]. In our study, sensory signs and symptoms were prominent (Table 2). Some toxins (such as organophosphates, hexacarbons and acrylamide) may have simultaneous toxic effects on both central and peripheral pathways (central-peripheral neuropathy) [17]. Brisk deep tendon reflexes which were observed among

our patients might reflect central involvement.

Toxins may have damaging effects on the peripheral nerves at different sites: on the axon, on the myelin sheath, on the cell bodies and on the vasa nervorum [2]. It already has been proven that one of the most common pathological manifestations of neurotoxin-induced axonal disease is selective vulnerability and degeneration of long and large axons [18]. In our study, electrodiagnostic examinations showed axonal involvement in 6 cases. Although electrodiagnostic studies were normal in other cases, the clinical examinations were definitely abnormal, which might indicate sensory neuropathy without any changes in electrodiagnostic studies.

The symptoms of our patients appeared with a delay phase of 17.5 years on average (Table 2). The pathophysiology of this delay type of neuropathy is not clear. It is known that some toxins such as organophosphates (OP) produce acute toxicity as well as delayed neurotoxicity which usually occurs 2-3 weeks after exposure. This neuropathy is predominantly motor, symmetrical, with muscle atrophy and pyramidal signs [19]. OP poisoning can induce acute toxic neuropathy in hens, which might be related to the disturbance of axoplasmic flow and axonal demyelination [20]. There is overwhelming evidence that modification of the structure of "neuropathy target esterase", by covalent binding of some organophosphorus esters, initiates an irreversible delayed polyneuropathy [21].

There is no proven treatment for toxic neuropathies. Some researchers used calcium channel blockers [22]. Clinicians should be aware of the possibilities of peripheral neuropathies, because it can significantly worsen after use of "non-toxic" dosages of known neurotoxic agents [23].

Sample size was the major limitation of this study. Further analytic cohort studies with appropriate sample size and specific focus on biopsy, and pathophysiology of the disease is recommended. It would also be interesting to evaluate neuropathy among American, British,

and Iraqi soldiers after Gulf War I and II and to evaluate the impacts of other toxic materials.

Acknowledgement

This study is sponsored by the Janbazan Medical & Engineering Research Center (JMERC). Authors appreciate the cooperation of the veterans in spite of their severe disabilities.

References

1. Pratt RW, Weimer LH. Medication and toxin-induced peripheral neuropathy. [Review]. *Seminars in Neurology* 2005; 25(2):204-16.
2. Neundorfer B. Toxic polyneuropathies. *Ver sicherungs Medizin* 1992. 44(4):119-25.
3. Clifton L, Louis H. The electrodiagnosis of neuropathy: basic principles and common pitfalls. *Neurol Clin* 2007; 25:1-28.
4. England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research. *Neurology* 2005; 64:199-207.
5. O'Donoghue JL, Nasr AN, Raleigh RL. Toxic neuropathy: an overview. *Journal of Occupational Medicine* 1919; 6: 379-82.
6. Reutter S. Hazards of chemical weapons release during war: new perspectives. *Environ Health Perspect* 1999; 107(12):985-90.
7. Wilson CM, Mackintosh JM. Mustard gas poisoning. *Q J Med* 1920. 13:210-239.
8. Murray VSG, Volans GV. Management of injuries due to chemical weapons. *Br Med J* 1991; 302:129-130.
9. Institute of Medicine. *Veterans at Risk: The health effects of mustard gas and Lewisite*. Washington, DC: National Academy Press; 1993. pp. 177-79.
10. Somani SM, Babu SR. Toxicodynamics of sulfur mustard. *Int J Clin Pharmacol* 1989;27:419-435.
11. Papirmeister B, Feister AJ, Robinson SI, Ford RD. *Medical Defense against Mustard Gas*. Boca Raton, FL: CRC Press; 1991. pp.2-3.
12. Marrs TC, Maynard RL, Sidell FR. *Chemical warfare agents, toxicology and treatment*. Chichester: John Wiley and Sons; 1996. pp. 376.
13. Balali M. Clinical and laboratory findings in Iranian fighters with chemical gas poisoning." In: *Proceedings of the world's first congress on biological and chemical warfare*, 21-23 May 1984, Ghent, Belgium. Ghent: Rijksuniversiteit; 1984. pp.254-259.
14. Balali-Mood M, Navaeian A. Clinical and paraclinical findings in 233 patients with sulfur mustard poi-

soning. In: Proceedings of new compounds in biological and chemical warfare. Second World Congress, International Association of Forensic Toxicologists, 23rd. European International Meeting, 24-27 August 1986, Ghent, Belgium. Ghent: Rijksuniversiteit; 1986. pp.464-473.

15. Requena L, Requena C, Sanchez M, Jaqueti G, et al. Chemical warfare: cutaneous lesions from mustard gas. *J Am Acad Dermatol* 1988. 19:529-536.

16. Bradley WG, Daroff RB, Fenichel GM. *Neurology in clinical practice*. 4th ed. Philadelphia: Butterworth-Heinemann; 2004. pp.1710-1714.

17. Katirji B, Kaminski H, Preston D.C. *Neuromuscular disorders in clinical practice*. 1st ed. Butterworth-Heinemann; 2002 .pp. 651-652

18. Serman, AB. The pathology of toxic axonal neuropathy: a clinical-experimental link. *Neurobehavioral Toxicology & Teratology* 1984.6(6): 463-6.

19. Carod-Artal FJ, Speck-Martins C. Late onset polyneuropathy due to exposure to organophosphates. *Revista de Neurologia* 1999; 29(2): 123-7.

20. Varsik P, et al. An acute toxic neuropathy caused by organo-phosphate poisoning in hens. *Bratislavske Lekarske Listy* 2004;105(3):91-4.

21. Johnson, MK. Organophosphates and delayed neuropathy: is NTE alive and well? [Review]. *Toxicology & Applied Pharmacology* 1990;102(3): 385-99.

22. El-Fawal HA, et al. Protease activity in brain, nerve, and muscle of hens given neuropathy-inducing organophosphates and a calcium channel blocker. *Toxicology & Applied Pharmacology* 1990; 103(1):133-42.

23. Chaudhry V, et al. Toxic neuropathy in patients with pre-existing neuropathy. *Neurology* 2003. 60(2): 337-40.