

Peripheral Neuropathy in Chemical Warfare Victims

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Citation

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Abstract

Objective: We aimed to assess the prevalence of peripheral neuropathy in chemical warfare victims (CWVs). We speculated that peripheral neuroathy (PN) is a late complication of exposure to chemical warfare agents (CWAs). Late complications of exposure to CWAs are not well known and are poorly discussed in the existing literature. Scientific data regarding delayed complications is sparse whereas it warrants recognition especially when the clinician has to treat CWVs. The hazards of organophosphate-pesticides and several toxins although recognized to some extent, are however, different from the hazards of CWAs which are far more serious.

Methods: In this study, 100 chemical warfare patients with varying degrees of exposure and an average age of 37.2 4.0 yrs. were examined clinically and studied electrodiagnostically.

Results: Five of these patients proved to be suffering from axonal neuropathy. This rate was significantly higher than that found in the normal population. Our data indicates that CWAs may cause PN in CWVs.

Conclusion: Organophosphorous (OP) agents used against Iranian troops during the war on Iran correlated with delayed neuropathy in these patients.

INTRODUCTION

During the Iraq-Iran war chemical warfare agents (CWAs) were widely used against Iranian troops by the Iraqis. This fact was confirmed by the international community in 1986 when a team headed by M. Dominguez verified Iran's claim. Other reports also documented Iraq's use of organophosphate nerve agents (especially Taboon) [1,2]. Despite the fact that Iran was victim to the massive use of CWAs, yet there is little information on the scope of serious harm caused by these agents.

The first, and probably most important report on this issue compiled by Hadrix from Sweden and Sohrabpour from Iran, was presented at a symposium held in 1985. One of the complications for which no definite link with chemical injuries has yet been established, is the issue of peripheral neuropathy (PN). This is despite the fact that the relationship between peripheral neuropathy and toxic agents, drugs and chemicals, [3,4,5,6,7,8] as well as genetic [3,4,5,6,7,8], nutritional, and metabolic diseases such as diabetes [3,4,5,6,7,8,9,10,11] have been documented. The link between CWAs and peripheral neuropathy is not well-defined. Consequently, most of the

information available tends to be related to the non-military use of these agents (accidental or occupational) for example, ophtalmopathy caused by organophosphates in herbicides and rodenticides [12]. Nonetheless, degeneration of the central nervous system (CNS) has been reported following constant exposure to these agents. Also, a syndrome called delayed neuropathic syndrome has been defined for those poisoned by organophosphates (organophosphate-induced delayed polyneuropathy or OPIDP) [13,14,15,16]. It should be added that organoarsenic agents and herbicides have also been reported to have triggered the degeneration of peripheral nerves leading to neuropathy. [13]

In light of the aforementioned studies, we selected a group of CWA victims to assess the prevalence of PN and to compare the findings of this disorder with the prevalence of peripheral neuropathy in the normal healthy population.

MATERIALS AND METHOD

A historical cohort study with an external control group was undertaken where all Iranian CWA victims of the Iraqi-imposed war were designated as the target population.

Iranian CWVs who referred to the clinic and met the inclusion criteria and did not have the exclusion criteria were recruited. Written consent for all the experiments and electrodiagnostics were obtained from all the subjects. The subjects underwent comprehensive tests including complete blood tests, biochemical tests, ophthalmologic tests, spirometry, and lung radiography. The inclusion criteria included the documentation and confirmation of CWA exposure by the medical commission of the Foundation For Injured or Disabled War Veterans, presence of chronic complications of chemical warfare agents such as ophthalmic, dermatologic, and symptoms exclusively attributed to CWA exposure. A history of physical trauma, systemic diseases responsible for neuropathy, exposure to toxins or use of drugs known to generate neuropathy constituted the exclusion criteria.

One hundred subjects were recruited in this study and a non-randomized sampling method from those available was utilized. The two methods of observation (measurement) and reference to existing profiles (file reading) were utilized. First, the subjects were visited by physical medicine and rehabilitation specialists, who completed the case history and conducted clinical neurological examinations. Next, the patients underwent electrodiagnostic tests, consisting of nerve conduction studies (NCS) and electromyography (EMG). The former measured latency, amplitude, and nerve conduction velocity (NCV) in the common peroneal, tibial, sural, superficial peroneal, median, ulnar and radial, nerves. The tibialis anterior and gastrocnemius muscles were evaluated for insertional activity, spontaneous activity, including positive sharpwaves, fibrillation, fasciculation, and neurogenic MUAPs. If positive findings were present, other muscles, including those of the upper limbs were also evaluated and if the patient had the inclusion criteria the diagnosis of PN was confirmed.

Relative frequency statistics, average relative frequency percentage, median, mode, standard deviation and variance range were used to work out the descriptive statistics. Whenever necessary, one sample test odds ratio, Chi-square and Z were applied. Type 1 error was 5% and the confidence interval was 95% (SPSS 9x was used to analyze the data).

RESULTS

The subjects selected for this study included 98 men and 2 women. While the majority of the participants in the study ranged from 29 to 70 years of age, the mean age was 37.2 years (+9.0). All the subject had been exposed to mustard

gas at least 10 years prior to the study, with an average time lapse of 13.3 years. The longest time lapse from the first exposure to mustard gas was 18 years and. 46.5% of the victims had been diagnosed as severely exposed; 30.3% had been moderately exposed and 23.2% had been slightly exposed to CWAs.

Clinical examination revealed that from a total of 100 individuals, 94% had cutaneous; 94% ophthalmic; 75% pulmonary; 5% digestive; and 10% hematological complications of CWAs. None of the patients had CNS problems. The results of the nerve conduction study (NCS) are presented in table 1.

Figure 1

Table 1: Mean latency, amplitude, and NCV of nerves in affected cases with neuropathy

	Latency(ms)		Amplitude (mV)		N.C.V. (m/s)	
	Rt	Lt	Rt	Lt	Rt	Lt
Common	5.7 (±.4)	6.0 (±0.3)	2.1 (±03)	1.8 (±0.2)	36 (±3)	38 (±2)
Peroneal						
Tibialis	5.2 (±0.8)	5.18 (±057)	1.9 (±0.1)	2 (±0.4)	35 (+2.5)	33 (2.8)
Posterior						
Sural	4.7 (±0.8)	4.2 (+0.2)	4 (±0.1)	5 (±09)	-----	-----
Superficial	4.3 (±0.3)	3.9 (±0.5)	4.8 (±03)	5.3 (0±.6)	-----	-----
Peroneal						
Median	3.7 (±0.33)	3.6 (±05)	23 (±2.2)	25 (±3.3)	-----	-----
(Sensory)						
Ulnar	3.9 (±0.22)	4.0 (±0.37)	16.7 (±3.3)	22 (±10.74)	-----	-----
(Sensory)						
Median	5.26 (±1.8)	4.9 (±2.9)	3.5 (±1.7)	3.0 (±0.3)	40 (±9.67)	42 (±4.7)
(Motor)						
Ulnar	4 (±02)	4.33 (±.3)	5 (±.55)	4.9 (±1.36)	44 (7±.1)	40 (±3.7)
(Motor)						

The figures derived from NCS and normal values evaluated by the t-test concluded that there was no significant difference between the data (P<0.05). In other words, the nerve conduction velocity in the victims was equal to that in the normal population. However, electromyography revealed that the findings were abnormal in 5 individuals as their insertional activities had increased and there was positive sharp waves (PSW) as well as fibrillations and neurogenic MUAPs. Such observations indicated the presence of axonal type peripheral neuropathy [3,4,5,6,7]. The mean age of these 5 patients was 49.8 years. Four of them suffered from severe chemical exposure (66.22%), and the other had slight exposure to chemical agents (20%).

A comparison between variables such as age, the interval between exposure to CWAS, the severity of chemical exposure in subjects having neuropathy and those without,

revealed that only age had a significant difference. The Mann-Whitney U-test showed that the age of the victims suffering from neuropathy was significantly higher than those not having such problems ($P = 0.004$). Nonetheless, the time lapse from exposure to chemical warfare agents and the percentage of exposure was not significant. Calculating the odds ratio in these patients revealed that victims with severe exposure were 4.09 times more likely to develop neuropathy than those with slight or moderate exposure. The only available statistic on idiopathic neuropathy related to Guillaine Barre (GB) is 0.4-1.7 in 100,000 (despite the fact that it is classified as acute neuritis). The incidence of neuropathy in those suffering from rheumatoid arthritis and diabetes is 1-5% and 2-4%, respectively. The Chi-square test revealed that the incidence of neuropathy was considerably higher among our subjects. In other words, statistics derived from this study are comparable to those related to neuropathy from pathologic processes.

DISCUSSION

Histological and electrophysiological features show that exposure to CWAs can cause axonal and myelin neuropathy in peripheral nerves. As there was no control group available for this study, available neuropathic statistics were applied for the purpose of comparison. The incidence of GB as an idiopathic neuropathy is 0.4-1.7/100,000. Researchers observed that the incidence of neuropathy in the victims under study was significantly different from that of arthritis rheumatic patients. However, it was not significantly different from that of diabetic patients. The presence of neuropathy in these victims indicates that there is a pathologic basis for it and can be regarded to be derived from chemical agents. Various insults are responsible for axonal neuropathy, some of which are trauma, ischemia, metabolic diseases, nutritional diseases (like diabetes, hypoglycemia, malabsorption, vitamin deficiency, etc.), some malignant diseases, various drugs and some systemic diseases. After predisposing diseases have been ruled out, drugs and toxins are the most probable causes. The prime suspects of such toxins are chemical compounds.

Organophosphate agents cause a delayed neuropathy which is called organophosphate induced delayed polyneuropathy (OPIDP). This arises in a delayed form after exposure to organophosphate agents. It is mainly motor neuropathy and is symmetrical, and sometimes associated with cerebellar atrophy and pyramidal syndrome [14,15,16,17]. OPIDP has long been recognized as a delayed process arising from exposure to organophosphate agents. Initially it had been related to the inhibitory effect of acetylcholinesterase enzyme [14]. Later

however, the findings of further researchers suggested that OPIDP was due to the neuro-toxic affects of organophosphate-agents. As a result, the significance of the disease and its causes were better understood from a new perspective [18,19,20]. Now, it is known that organophosphates and some of their derivations bring about neurotoxic effects by an agent called neuropathy target esterase (NTE). NTE is a membrane protein present in all neurons. The role of NTE is in the pathway which controls reactions between the neurons and glial cells. Organophosphorous, when combined with NTE, causes unknown incidents that after several weeks delay, bring about neuropathy and degeneration in axons. OPIDP is indeed presented as a model for identifying an incidence called promotion. It refers to the aggravation of clinical syndromes, and traumatic and toxic morphological neuropathies, which seem to be caused by esterase inhibitors and NTE as a modulator. [21,22,23,24,25,26,27,28].

Electrodiagnostic studies indicated that the victims under study were suffering from axonal neuropathy. The pattern of involvement in our cases was identical to the description of Amato and Dumitru [29]. Although it is not possible to determine the scope of pathological damage by this test, however, the electrodiagnostic patterns indicated that the :“dying back!” can be regarded as the influential mechanism. On the other hand, injection of a single dose of organophosphorous in hens revealed that it causes OPIDP. It was also found that OPIDP is not necessarily dependent on previous noxiousness. It was observed that sublethal and chronic doses can cause OPID as well [15]. These findings make for a strong question regarding the previous notion that there is no possibility for OPIDP to take place by noxiousness of chemical warfare agents [14]. It must be mentioned, however, that the most severe form of neuropathy can be observed in noxiousness with organophosphorous combinations, and most of the victims having been previously exposed to organophosphorous agents suffered from imperceptible peripheral nerve complications such as increament of perception and vibration threshold [27]. In other words, the absence of polyneuropathy does not necessarily mean that the effect of chemical war agents can be disregarded. Rather, it is necessary to resort to better methods for assessment.

Another important point is the average age of the victims suffering from polyneuropathy compared to those not suffering from this problem. Regarding OPIDP, it has been observed that birds and rats lose their resistance against neuropathy by aging [26]. The same is true for increment

perception and vibration threshold [27]. There are a limited number of studies in which warfare agents have been assessed. Organophosphorous agents have caused neurotoxicity in poultry. Some of the human observations of these agents, confirmed the findings derived from studies using nonmilitary agents [13]. Considering the consistency of the findings of the studies mentioned above and the findings of this study, we suspect that noxiousness in cases in this study are due to exposure to this agent. Nerve biopsy can precisely show pathologic features of the lesion. NET is a supreme biochemical marker for OPIDP screening and some biosensors have been developed for this aim. [28]. By applying all these recognition methods, the role of neural factors in causing these neuropathies can be better determined. Further studies are under way to further address this issue.

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