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Electrophysiological Changes in Patients with Acute Organophosphorous Pesticide Poisoning

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Abstract: Organophosphorous pesticides (OP) are widely used in agriculture without proper control in the Islamic Republic of Iran and thus OP poisonings are common in this country. Epidemiological and management aspects of OP have been studied in detail, but there have been very few reports on peripheral polyneuropathy, particularly electrophysiological changes related to this poisoning. Thus, we aimed to study electrophysiological changes including electromyography (EMG) and nerve conduction velocity (NCV) in patients with OP poisoning. The patients with acute moderate to severe OP poisonings who revealed clinical symptoms and signs of peripheral polyneuropathy after recovery of the acute phase of intoxication were investigated from 2005 to 2006 in Mashhad, Iran. These patients lacked previous neurological problems and had not been chronically exposed to OP. EMG and NCV were performed using MEDELEC MS92 & TOENNIES Multiliner E. Statistical analyses including Student's *t*-test and Pearson's test were applied using SPSS (Version 11.5). Of 342 hospitalized patients, eight patients (four females and four males) aged 13–59 years were investigated. Intervals between the onset of OP poisoning and electrodiagnostic tests varied between 10 and 210 days. On EMG, there was a sensory-motor peripheral polyneuropathy, which was predominantly a distal sensory deficit. Sensory nerve dysfunction (84.4%) was significantly higher ($p < 0.001$) than motor dysfunctions (18.7%). The lower extremities, particularly tibial and peroneal nerves, were more affected than the upper extremities ($p < 0.0001$). Sensory nerve dysfunction of the lower extremities was more common than motor nerves, which was predominantly a distal sensory deficit.

Organophosphorous pesticides (OP) are widely used in many parts of the world. OP are used for agricultural purposes in the Islamic Republic of Iran without proper control and thus OP poisonings are common in this country [1,2].

Worldwide, it is estimated that 3,000,000 people are exposed to organophosphate or carbamate agents each year, with up to 300,000 fatalities [3–5].

OP belong to the group of anticholinesterase agents that inhibit acetylcholine (ACh) hydrolysis. Accumulation of ACh results in stimulation of the muscarinic and nicotinic receptors which induces clinical manifestations. However, neurotoxic effects of OP may be because of neuropathy target esterase (NTE) pathway disturbances [3,4,6].

OP-induced delayed neuropathy (OPIDN) is a symmetrical sensory-motor neuropathy, tending to be the most severe in long axons and occurring some weeks after exposure. In severe cases, it is an extremely disabling condition [3,4]. In one study, no or mild symptoms or signs compatible with cholinergic overstimulation were reported in the patients [7].

It seems that the development of OPIDN depends on the inhibition of NTE. However, other mechanisms may be involved. A trophic factor (ornithine decarboxylase), which is a growth-related enzyme, was decreased in the spinal cord following the neuropathic agent, diisopropylfluorophosphate [5].

Several OP that are not currently used as pesticides in the developed countries, such as mipafox, diisopropylfluorophosphate and leptophos, have repeatedly been reported to produce OPIDN [8].

Affected patients present with transient, painful 'stocking-glove' paraesthesia followed by a symmetrical motor polyneuropathy characterized by flaccid weakness of the lower extremities, which ascends to involve the upper extremities [8,9]. Kaplan reported eight patients with sensory neuropathy and CNS dysfunction after acute chorpyrophos poisoning [7].

Sensory disturbances are usually mild. Delayed neurotoxicity primarily affects distal muscle groups, but in severe neurotoxicity, proximal muscle groups may also be affected [9]. In a study with eight patients exposed to chlorpyrifos (dursban), it was concluded that environmental contact with this agent can cause sensory neuropathy and CNS dysfunction [7,10].

OP that react with NTE *in vivo* initiate unknown events which lead, after a delay of 1–3 weeks, to a neuropathy with degeneration of long axons [11].

Signs include high-stepping gait associated with bilateral foot drop and, in severe cases, quadriplegia with foot and wrist drop as well as pyramidal signs. In time, there might be

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significant recovery of the peripheral nerve function but, depending on the degree of pyramidal involvement, spastic ataxia may be a permanent outcome of severe OPIDN [12].

Electromyograms and nerve conduction studies of affected patients have revealed decreased firing of motor conduction units [13]. Histopathological sections of peripheral nerves have revealed Wallerian or 'dying back' degeneration of large distal axons [14].

Suggested diagnostic criteria for the OPIDN syndrome include the following:

1. History of severe acute organophosphate poisoning about 1–6 weeks prior to the onset.
2. Symptoms and signs of polyneuropathy and later with or without concurrent pyramidal signs.
3. Denervation changes established by electromyography (EMG).
4. Slow recovery.
5. Reasonable exclusion of other nervous diseases [15].

There have been very few reports on the EMG and nerve conduction velocity (NCV) changes in patients with OP poisoning. Thus, we aimed to study the electrophysiological changes in patients with acute OP poisoning.

Material and Methods

The patients with intentional acute moderate to severe OP poisonings after recovery of the acute phase of intoxication were investigated between 21 March 2005 and 20 March 2006 in Mashhad, Iran. Diagnosis of OP poisoning was based on the history of OP ingestion, clinical manifestations and decreased acetylcholine esterase (AChE) activity. Type of OP was only recognized based on presentation of the labels on the OP bottles. The patients who had cholinergic syndrome and CNS depression without respiratory failure were defined as moderate and those with respiratory failure, who needed mechanical ventilation were marked severe OP poisoning [16]. All severely intoxicated patients were treated in the intensive care unit of the centre.

After clinical recovery of the acute OP intoxication, the patients with clinical signs or symptoms of muscle weakness or peripheral neuropathy such as paraesthesia, numbness and tendon/plantar reflex dysfunctions were referred to Kian electrodiagnostic laboratory following obtaining informed consent. A complete medical history consisting of clinical findings and paramedical investigations was obtained for each patient to rule out other neurological diseases or even co-existing diseases like acquired or inherited neurogenic or myogenic problems. Patients who ingested alcohol or any other chemicals and pharmaceuticals as well as patients with chronic OP exposure were excluded.

EMG and NCV were performed using an EMG machine (MEDELEC MS92 & TOENNIES Multiliner E). Diagnostic tests consisted of nerve conduction studies of different limb nerves and EMG of the related muscles.

Firstly, by using surface electrodes, sensory and motor NCV was obtained on four nerves (Median, Ulnar, Peroneal and Tibialis). We used an orthodromic method for measuring sensory latency. For motor NCV, after proximal and distal stimulation by surface excitatory electrode, the difference in time latencies was divided by the distance of the two excitation points.

Secondly, EMG was performed. For this purpose, we used sterile needle electrodes to obtain myograms of muscles including biceps, extensor digitorum communis from hands, quadriceps, anterior tibialis and gastrecnemius from legs. The patient was asked to be relaxed; then the concentric needle was pushed deeply into the muscle, and after assuring that no spontaneous wave would occur, the patient was asked to contract his/her muscle maximally. The two important parameters, amplitude and duration of waves were analysed. These were needed to distinguish between myogenic and neurogenic patterns. All EMG and NCV tests were performed 3 times for each patient on the same day. Duration between each EMG and NCV test was only a few minutes. The median of the three measurements was considered for the statistical analyses.

The results are shown as means and standard deviations. Statistical analyses including Student's *t*-test and Pearson's test were applied using SPSS (Version 11.5, Chicago, IL, USA). $p < 0.05$ was considered as the statistically significant level.

Results

Of 342 patients with moderate to severe OP poisonings who were hospitalized in the Poisons Treatment Unit of Imam Reza hospital, eight patients (four males and four females) aged 13–59 (22.75 ± 14.97) who showed clinical signs of peripheral polyneuropathy or muscle weakness were studied. Seven identified OP types were recorded from the labelled bottles, being chlorpyrifos (three cases), malathion (two cases) and azinphosmethyl (two cases).

Clinical and electrophysiological findings of the eight patients are summarized in table 1. Based on overall clinical severity grading of poisoning [16], three patients had

Table 1.
Summary of clinical and electrophysiological findings in eight patients with acute OP poisoning.

Case number	1	2	3	4	5	6	7	8
Sex	M	M	M	F	F	F	M	F
Age (year)	19	59	17	21	13	17	22	14
OP Type	AM	MT	CP	MT	AM	CP	CP	N/A
Poisoning severity	S	M	S	S	S	S	M	M
Lowest AchE (U/ml)	0.5	1.2	0.5	<0.5	<0.5	0.8	1.6	2.4
Discharge AchE (U/ml)	1.5	2.7	1.4	1	1.1	1.7	3.1	3.5
Test day AchE (U/ml)	N/A	2.7	N/A	N/A	N/A	N/A	3.1	3.5
Hospitalization days	31	10	34	30	50	19	14	10
ICU days	9	0	3	5	26	3	2	3
Mechanical ventilation	+	–	+	+	+	+	–	–
Motor dysfunction	+	–	+	+	+	–	–	–
Sensory dysfunction	+	++	++	+	+++	++	++	+

AM, azinphos-methyl; MT, malathion; CP, chlorpyrofos; N/A, not available; ICU, intensive care unit; OP, organophosphorous pesticides.

moderate and five patients had severe intoxication, of which three presented with intermediate syndrome. AChE activity was below the minimum normal level (4.2 U/ml) on admission and varied between 0.5 and 3.5 U/ml during treatment. Reactivation of AChE was slow and did not reach the minimum normal level of up to 7 weeks. There was a highly significant negative correlation between the severity of poisoning and AChE activity ($p < 0.0001$).

All patients received standard treatment of OP poisoning (atropine sulfate, pralidoxime and sodium bicarbonate), supportive and intensive care therapy. Only one patient (case no. 2; table 1) with moderate OP poisoning did not need admission to the intensive care unit. Clinical improvement occurred earlier than the AChE reactivation, and the patient was discharged based on clinical improvement but not complete AChE reactivation.

Intervals between the onset of OP poisoning and electrodiagnostic tests varied between 10 and 210 days. Three of the eight patients were tested during hospitalization or <1 week after discharge. Four patients were referred back to our centre by their family doctors within 6 weeks after OP exposure because of clinical signs of peripheral polyneuropathy or muscle weakness. The 8th patient was referred to us more than 6 months after discharge (210 days after OP exposure) by a neurologist who could not establish any other aetiology than the previous OP poisoning for the peripheral polyneuropathy in this particular patient.

On EMG, a sensory-motor peripheral polyneuropathy was identified which was predominantly categorized as a distal sensory deficit.

NCV of the right and left median, ulnar, tibial and peroneal nerves in the eight patients with OP poisoning in comparison with the normal values [17] are shown in table 2. As is evident, NCV of left ulnar was the highest (65.6 ± 3.15 m/s) and the left tibial was the lowest (44.6 ± 10.04 m/s). The NCV of the left ulnar was significantly ($p = 0.034$) higher than normal value, but there were no statistically significant differences in other upper limb nerves. In lower limbs, both right and left tibial, NCVs were significantly ($p = 0.04$ and 0.023, respectively) lower than the normal values.

Table 2.

NCVs of each nerve (m/s) in eight patients with acute OP poisoning compared to normal values [20].

Nerves	Mean ± S.D.	Normal value	*p* value
R.Median	59 ± 6.07	56.7 ± 3.8	0.319
L.Median	59.4 ± 7.61	56.7 ± 3.8	0.375
R.Ulnar	64.4 ± 3.15	62.7 ± 5.5	0.128
L.Ulnar	65.6 ± 3.15	62.7 ± 5.5	**0.034**
R.Tibial	46.8 ± 9.16	54.9 ± 7.6	**0.04**
L.Tibial	44.6 ± 10.04	54.9 ± 7.6	**0.023**
R.Peroneal	47.4 ± 10.21	51.6 ± 4.1	0.294
L.Peroneal	48.7 ± 9.00	51.6 ± 4.1	0.137

NCV, nerve conduction velocity; OP, organophosphorous pesticides.

Table 3.

Sensory latencies of each nerve (ms) in eight patients with acute OP poisoning compared to normal values [20].

Nerves	Mean ± S.D.	Normal value	*p* value
R.Median	4.2 ± 0.71	2.4 ± 0.3	<0.0001
L.Median	3.77 ± 0.54	2.4 ± 0.3	<0.0001
R.Ulnar	3.23 ± 0.76	2.4 ± 0.3	=0.017
L.Ulnar	3.37 ± 0.63	2.4 ± 0.3	=0.003
R.Tibial	5.41 ± 0.83	3.5 ± 0.2	<0.0001
L.Tibial	5.22 ± 0.96	3.5 ± 0.2	=0.001
R.Peroneal	4.82 ± 0.75	2.9 ± 0.3	<0.0001
L.Peroneal	4.61 ± 0.64	2.9 ± 0.3	=0.004

OP, Organophosphorous pesticides.

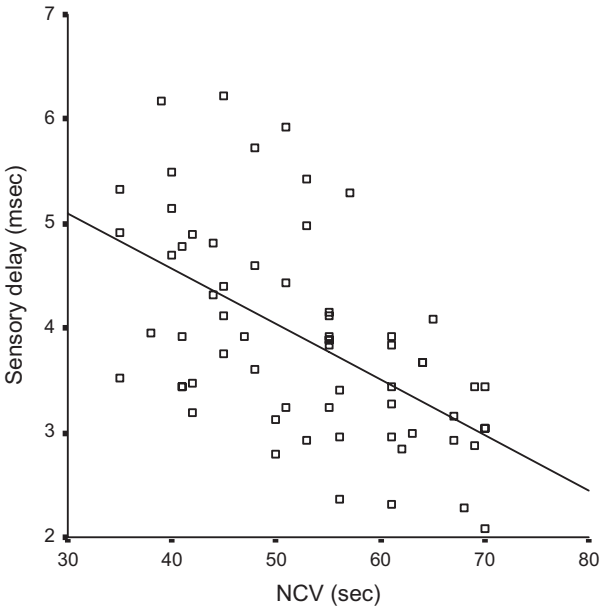

Fig. 1. Correlation between sensory latency and nerve conduction velocity in eight patients with acute OP poisoning ($r^2 = 0.312$, $p < 0.0001$).

Sensory latency of the related nerves and the normal values [17] are illustrated in table 3. As shown, sensory nerve latency of the right ulnar was the lowest (3.23 ± 0.76 ms) and the right tibial was the highest (5.41 ± 0.83 ms). There was a highly significantly negative correlation ($r = -0.558$, $r^2 = 0.312$, $p < 0.0001$) between the motor nerve dysfunction and sensory nerve latency as illustrated in fig. 1.

Three patients had no sensory response for the right tibial nerve in two of three measurements; this result only was used in the statistical analyses.

Wave's amplitudes were all below the average normal reference values [17]. The results are shown in table 4.

Another finding was the highly significant differences ($p < 0.0001$) between the upper and lower limbs both in motor NCV (upper = 62.1 ± 3.38 m/s and lower = 55.77 ± 5.86 m/s) and sensory nerve latencies (upper = 3.35 ± 0.47 ms and lower = 4.33 ± 0.64 ms).

Table 4.
Amplitude of waves (mV) for both sensory and motor nerves in eight patients with acute OP poisoning compared to normal values [20].

	Nerves	Mean ± S.D.	Normal values	*p* value
Motor	Median	9.14 ± 1.86	13.2 ± 0.5	<0.0001
	Ulnar	3.8 ± 1.4	5.8 ± 1.5	<0.0001
	Tibial	2.3 ± 0.5	8.8 ± 3.4	<0.0001
	Peroneal	2.1 ± 0.39	3.9 ± 1.2	<0.0001
Sensory	Median	8.08 ± 3.2	15–50	*
	Ulnar	15.9 ± 3.56	15–50	*
	Tibial	6.02 ± 1.34	10–50	*
	Peroneal	7.3 ± 2.19	10.5 ± 6.1	<0.0001

OP, organophosphorous pesticides.
*No *p* value could be calculated because of the lacking mean reference value.

There was no statistically significant correlation between the clinical severity or AchE activity and the electrophysiological changes.

Discussion

Our study revealed clinical signs of peripheral polyneuropathy after moderate and severe acute OP poisoning in a small number of patients (8 of 342; 0.023%).

The electrophysiological findings in the study showed more sensory nerve involvement. Our findings are compatible with the two reports of Kaplan *et al.* [7] and Luiz Felipe *et al.* [13].

The motor component of polyneuropathy was not noticeable. Although Moretto and Lotti [10] searched for sensory polyneuropathy in 11 patients with acute OP poisoning and the title of their report is sensory neuropathy, they failed to show this, and they found more motor involvement than the sensory deficit. They then explained that sensory neuropathy may occur after moderate to severe OP poisoning. If sensory polyneuropathy develops after mild acute OP poisoning, other causes of sensory polyneuropathy should be sought [10].

Clinical presentation of acute OP poisonings usually reveals cholinergic crises, CNS depression and less often intermediate syndrome consisting of skeletal muscle weakness and paralysis leading to respiratory failure [5,6,8]. In this study, only three patients revealed clinical symptoms of intermediate syndrome, and thus we could not find any relationship between the intermediate syndrome and OPIDN.

A review of the literature described a nervous system disorder induced by chronic exposure to OP which involves neuronal degeneration and subsequent neurological, neurobehavioural and neuropsychological degeneration [9]. It seems that delayed peripheral polyneuropathy is more common after acute OP poisoning than after chronic exposure, whereas chronic neuropsychiatric disorder is more common after chronic OP exposure than after acute OP poisoning [15].

Routes of OP entry to the body are mainly inhalational, oral and through the skin, but other forms, however, rare, like parenteral (self-injection) of malathion have also been reported leading to delayed polyneuropathy [18]. Acute OP poisoning mostly occurs after suicidal attempt by oral ingestion, whereas chronic exposure usually follows inhalational or dermal absorption.

For some motor neuron diseases, the genetic role seems to be the major determinant of disease initiation. In these genetic motor neuron diseases and OPIDN, NTE pathway disturbances contribute to initiation and progression of the disease. Considering phenotypic similarities together with the identified association of paraoxonase polymorphisms with amyotrophic lateral sclerosis, there is a possibility that neurotoxic substances such as OP contribute to motor neuron diseases in genetically vulnerable individuals by means of gene–environment interactions [19].

Our findings show that the amplitude of waves was abnormal for both sensory and motor nerves with diffuse and non-specific abnormalities in the upper and lower extremities. We were unable to find any relationship between the severity grading of intoxication and the amplitude of waves because of the low number of patients.

It is of interest that the nerve dysfunction in both motor NCV and sensory latencies was significantly different between the upper and lower extremities.

NCV of the upper limbs was higher than of lower limbs, but the sensory latencies of the upper limbs were less than of the lower limbs. This could probably be because of the length of the nerves which is greater in lower than in upper limbs and thus the damage can be more diffuse in longer nerves. We were unable to find any similar reported data to compare with these findings.

NCV of the left ulnar nerve was significantly higher than the normal value, whereas the right ulnar and both right and left median nerves did not show any significant differences. We have no explanation for this discrepancy; however, it might be the reason for the significant difference between the upper and lower limb NCV.

The sensory latencies revealed more harmonized results. Again, we did not find any similar reported data to compare with our findings.

In two human studies, the concomitant ingestion of alcohol has been shown to enhance the toxic effects of Diptrex (trichlorofon) [20,21]. We had already excluded co-ingestion of alcohol or any other chemicals or pharmaceuticals. However, the role of alcohol or any other chemical substances in acceleration or reduction of human toxicity remains unknown and need to be further studied.

Conclusion

This study suggests that:

1. Peripheral delayed neuropathy may occur after acute OP poisoning.

2. The major clinical and electrophysiological nerve dysfunctions were mostly sensory deficit. Sensory and motor

dysfunctions were more significant in the lower extremities than in the upper extremities.

Limitations of the Study

1. The power of this study might be inevitably limited for some of the scarce findings.

2. There was no control group; thus, the comparisons were made based on the reference values.

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