

Late Onset Polyneuropathy due to Organophosphate (DDVP) Intoxication

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ABSTRACT: Background: Organophosphate intoxication can cause some well-known life threatening acute neurological complications such as seizures, paralysis, neuromuscular and cardiac conduction disorders. Less often, a predominantly motor and delayed axonal neuropathy can occur. This syndrome is due to inhibition of neuropathy target esterase. **Case Report:** A 30-year-old woman attempted suicide by drinking approximately 1000mg/kg dimethyl-2,2-dichloro vinyl phosphate (DDVP). After a muscarinic and cholinergic syndrome lasting four days, she developed a purely motor distal axonal polyneuropathy on the fifth week after ingestion confirmed by electroneuromyography and sural nerve biopsy. Neurological examination and electroneuromyography revealed a slight recovery at the end of the 21st month. **Conclusion:** This case of late onset polyneuropathy caused by organophosphate intoxication had unusual features such as intact sensory nerves and worse prognosis when compared to previously reported cases.

RÉSUMÉ: Polyneuropathie tardive due à une intoxication par un organophosphoré. Contexte: L'intoxication par les organophosphorés peut causer des complications neurologiques aiguës pouvant mettre la vie en danger, telles des convulsions, une paralysie, des troubles de conduction neuromusculaires et cardiaques. Plus rarement, une neuropathie à prédominance motrice et axonale peut survenir. Ce syndrome est dû à l'inhibition de la neuropathy target esterase. Observation clinique: Une femme âgée de 30 ans a fait une tentative de suicide par ingestion d'un peu près 1 000mg/kg de 2,2 dichlorovinyl diméthyl phosphate. Suite à un syndrome muscarinique et cholinergique de quatre jours, elle a développé une polyneuropathie axonale distale purement motrice la cinquième semaine après l'ingestion, neuropathie confirmée par électroneuromyographie et biopsie du nerf sural. L'examen neurologique et l'électroneuromyographie ont montré une légère récupération après 21 mois. **Conclusion:** Ce cas de polyneuropathie à début tardif causée par une intoxication par un organophosphoré était caractérisé par des nerfs sensitifs intacts et un pronostic plus sombre que les cas rapportés antérieurement.

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Organophosphates are still widely used in developing countries for agriculture and industry. They produce irreversible inhibition of acetylcholinesterase, resulting in depolarising block at muscarinic and nicotinic synapses in insects as well as humans. Some well-known life threatening acute neurological complications of organophosphates are seizures, paralysis, and neuromuscular and cardiac conduction disorders. Early administration of atropine and pralidoxime and supportive care are of paramount importance in treatment of acute syndrome.¹ Delayed neuropathy is a rare complication of organophosphate poisoning and a result of inhibition of neuropathy target esterase instead of acetylcholinesterase. Among many thousands, only a small number of organophosphates can produce polyneuropathy with delayed onset. Organophosphate compounds that are known to produce distal axonal polyneuropathy in humans are triorthocresyl phosphate,² leptophos,³ mipafox,⁴ trichlorofon,⁵ merphos,⁶ diptelay,⁷ systox,⁸ mecarbam,⁹ methamidophos,¹⁰ and chlorpyrifos.¹¹

CASE REPORT

A 30-year-old, 54-kg female farm worker, who had been previously treated for major depression, attempted suicide by drinking about 100cc of a commercial fluid emulsion of 55% DDVP (DIDIFOS® 55 EC; Hektas). She was comatose, with bilateral miosis and was unresponsive to deep pain when she was brought to the emergency department at the fourth hour after ingestion. Sinus tachycardia, excessive sweating, frothy whitish oral and nasal secretions, urinary incontinence and twitching of the extremities were noted. Routine biochemical tests were normal

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Table 1: Serial results of some sensory nerve conduction values on the right side of the patient.

Nerve	Segment	Sensory Conduction Studies						
		CNAP-A(μ V)					Velocity (m/sec)	
		N	Day 42	Day 275	Day 384	Day 678	N	Day 42/Day 687
median	digit II-wrist	≥ 11.4	18.1	15.8	19.2	18.0	≥ 48.2	55.3/56.5
ulnar	digit V-wrist	≥ 6.1	14.0	14.1	15.6	16.1	≥ 46.9	52.6/51.3
sural	calf-l. malleolus	≥ 6.9	11.1	10.6	9.3	10.5	≥ 40.3	42.6/42.6
s. peroneal	calf-l. ankle	≥ 6.1	9.2	7.9	8.4	8.4	≥ 41.4	45.6/46.4

CNAP-A = Compound nerve action potential amplitude; μ V = microvolt; m/sec = meter/second; N = normal limits of the patient's age group and gender of our laboratory; l. malleolus = lateral malleolus; l. ankle = lateral ankle; s. peroneal = superficial peroneal (The given amplitudes were measured peak to peak).

except for rises of creatine kinase up to 400 U/L and lactate dehydrogenase to 312 U/L. Gastric lavage, atropine administration and ventilatory support were carried out initially. She was comatose for four days, then improved progressively from day 5 to day 17 and was asymptomatic by day 18. The neurological examination was normal at that time and she was discharged out of the hospital. She did not have any additional cardiac, renal or gastrointestinal problems in the course of improvement. However, five weeks after intoxication she began to complain of weakness of her feet and difficulty in walking. Cranial nerves were intact. She exhibited moderate weakness of ankle and toe dorsiflexors and intrinsic foot muscles and slight weakness of proximal leg and hand muscles with impaired gait on examination. The Achilles reflexes were absent and other deep tendon reflexes were symmetrically reduced. Pain, temperature, tactile, position, vibration and pressure sensations were all normal. Electrophysiological studies (day 42) demonstrated a purely motor symmetrical axonal polyneuropathy that was predominant in the legs. Sensory nerve conduction studies (median, ulnar, lateral and medial antebrachial, sural and superficial peroneal nerves on both sides) were all normal (Table 1). The compound motor action potentials (CMAPs) could not be elicited from extensor digitorum brevis muscles by stimulating the peroneal nerves. Severe reduction of CMAP amplitudes were noted in response to stimulation of posterior tibial nerve and there was a moderate reduction in response to median nerve stimulation (Table 2). Increased insertional activity, prominent

fibrillations and positive waves, discrete polyphasic motor unit potentials were observed in distal and intermediate muscles of both legs (adductor longus, vastus lateralis, tibialis anterior, medial head of gastrocnemius, extensor hallucis longus and abductor hallucis muscles were investigated on both sides). Hand muscles exhibited milder evidence of subacute axonal neuropathy in which rare fibrillations and positive waves and polyphasic motor unit potentials with reduced interference pattern were observed (deltoid, biceps, triceps, first dorsal interosseus and abductor pollicis brevis muscles were investigated on both sides). Magnetic resonance imaging of the brain, routine biochemical tests and cell count of cerebrospinal fluid, EEG and visual evoked potentials were normal. Biochemical investigations ruled out other causes of polyneuropathy such as diabetes, uraemia and porphyria. The sural nerve biopsy specimen studied both by semi-thin light and electron microscopy on day 110 was normal (Figure 1 and Figure 2). Serial evaluations of the patient within the first nine months did not disclose any improvement or deterioration in clinical or electrophysiological findings except for the development of mild atrophy and some chronic motor unit potential changes in distal muscles of the limbs. The clinical and electrophysiological follow-up examinations performed at days 274, 384 and 678 after intoxication revealed mild improvement in weakness, atrophy and nerve conduction studies of upper and lower extremities respectively (Table 1). There was no evidence of upper motor neuron involvement.

Table 2: Serial results of some motor nerve conduction values on the right side of the patient.

Nerve	Recording site	Motor Conduction Studies						
		CMAP-A(mV)					Velocity (m/sec)	
		N	Day 42	Day 275	Day 384	Day 678	N	Day 42/Day 687
median	APB	≥ 5.1	1.8	3.5	4.5	4.9	≥ 52.0	54.7/57.7
ulnar	ADM	≥ 6.4	4.9	7.2	7.5	8.1	≥ 50.8	61.5/62.6
tibial	TA	≥ 4.2	0.1	0.2	0.7	0.8	≥ 41.9	-/44.8
c. peroneal	EDB	≥ 2.3	NP	NP	0.2	0.2	-	-/-

CMAP-A = Compound motor action potentials; mV = millivolt; m/sec = meter/second; N = normal limits of the patient's age group and gender of our laboratory; APB = abductor pollicis brevis; ADM = abductor digiti minimi; TA = tibialis anterior; EDB = Extensor digitorum brevis; NP = no potential; c. peroneal = common peroneal; -=distrustful because of low CNAP-A; (The given velocities are between elbow-wrist for median and ulnar; popliteal fossa-ankle for posterior tibial and fibular head-ankle for peroneal nerves).

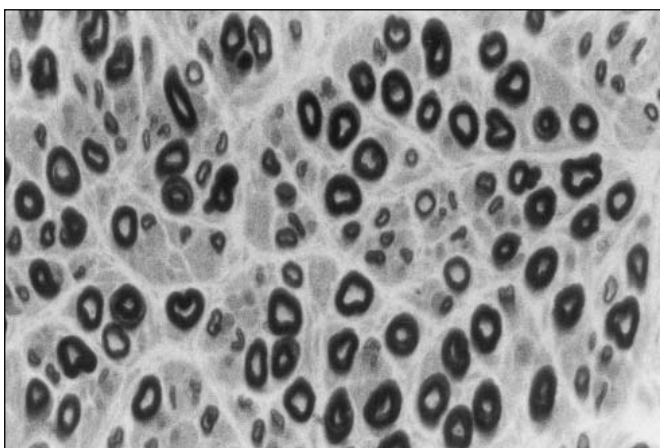


Figure 1: Normal semi-thin light micrograph (original magnification $\times 400$) of the sural nerve on day 110 showing the horizontal sections of both myelinated and unmyelinated axons. The perineurium and blood vessels are also observed.

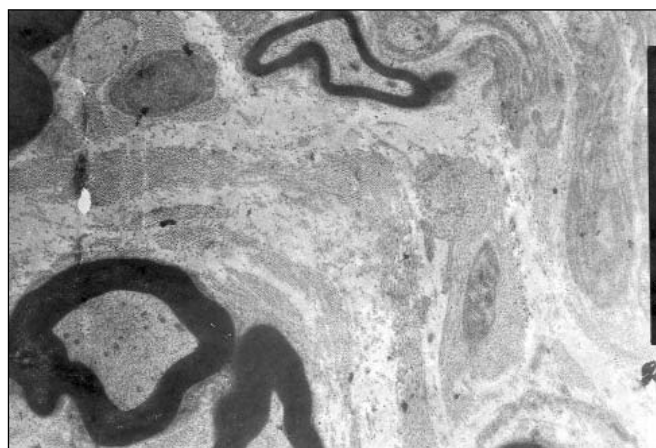


Figure 2: Normal electron micrograph (original magnification $\times 3000$) of the sural nerve on day 110.

DISCUSSION

Organophosphate-induced delayed polyneuropathy (OPIDP) is postulated to be initiated by inhibition or modification of a target membrane-bound protein, which is also known as neuropathy target esterase (NTE).¹²⁻¹⁵ The physiological function of NTE is unknown, but it has been shown to be reduced in the nervous system of susceptible animal species and humans exposed to certain organophosphates.¹⁶⁻²⁰ According to this hypothesis, intensive phosphorylation of NTE occurs in the axons and the cascade continues with the second step called “aging”. “Aging” refers to the separation of an alkyl group from the phosphorus, leaving a negatively charged phosphoryl group attached to NTE. Only compounds capable of “aging” can cause a polyneuropathy.¹⁶ The potency of an organophosphate to cause OPIDP is related to the chemistry of the residue left attached to NTE and its affinity for the enzyme.¹⁷ This rapid reaction is not enzyme dependent and requires a high level of NTE inhibition in experimental animals (70%). The threshold in man is not known but may be similar. The “aged phosphoryl-NTE complex” selectively inhibits the retrograde axonal transport defined as “chemical transection” and causes a delayed polyneuropathy. NTE has also been proposed to be a predictive marker in organophosphate intoxication for subsequent development of OPIDP in hens and in humans.²¹ A pathological study demonstrated that the type of neuropathy caused by organophosphates in cats is “focal distal but not terminal axonal degeneration”.^{22,23} In the last decade, however, some authors postulated that this original NTE hypothesis requires modification as non-neuropathic inhibitors of NTE exist and can actually prevent OPIDP when given before a neuropathic organophosphate; in addition, these agents can intensify or potentiate signs of OPIDP in chickens when administered after exposure (promotion of OPIDP).²⁴ Lotti and his co-workers²⁵ suggested that promotion of neuropathy was likely to be due to interactions with another unknown target instead of NTE and that a more complex model should be considered. Johnson²⁶ described the unknown target as ‘cousin of NTE’ because he

suggests that it should have very similar inhibition characteristics with NTE and might be linked to NTE. Vilanova et al²⁷ had a possible explanation for this and proposed one of the isoforms of NTE (S-NTE 2) as a target of promotion.

Our patient had several unusual features when compared with the cases of OPIDP reported before. We did not encounter reports of delayed polyneuropathy due to DDVP in humans, nor an experimental study involving DDVP. Moretto and his co-workers²⁸⁻³⁰ examined experimental animals with a similar compound, di-n-butyl dichlorovinyl phosphate, which they define as a potent organophosphate for causing delayed polyneuropathy. Our case is probably the first reported OPIDP due to DDVP. The onset of polyneuropathy was five weeks after exposure which was longer than most of the reported cases. Lotti et al²³ reported a patient in whom the onset occurred six weeks after ingestion of chlorpyrifos and concluded that slow disposal of a massive dose could be the reason for the unusual delay of onset. In the literature, there is a direct correlation between the duration of coma and the delay in onset of polyneuropathy.^{31,32} In our case, however, the delay in onset of polyneuropathy was longer than for the patient's duration of coma (four days). There may be an additional determining factor (for instance, the type of organophosphorus compound and its amount) that accounts for the delay of onset. The normal serial sensory nerve conduction studies in our patient were similarly unusual. Motor predominance of axonal degeneration is a well-known feature of OPIDP, but normal sensory nerve conduction studies are rare. Of more than 100 cases with OPIDP in the literature, only two had normal sensory nerve conduction studies, but sensory nerve biopsy was not performed in these two patients.^{31,33} Considering the wide range of the normal values, electrophysiological studies may not be sensitive enough to completely exclude sensory involvement. The sural nerve biopsy in our patient was normal. Thus, the site of degeneration was motor axons or motor neurons, yielding a “purely motor axonal polyneuropathy” or “motor neuronopathy due to organophosphate intoxication”. The prognosis of OPIDP in our case was worse than expected.^{9,11,32} Unlike previous reports, after nine months we observed mild

improvement of muscle strength and electrophysiological findings in upper limbs and saw similar results after 13 months in the lower extremities. This may suggest a proximal lesion and the long-time course may suggest that axonal regeneration or collateral sprouting of residual motor axons account for the recovery we identified.

Our case report illustrates that DDVP intoxication can result in a largely irreversible purely motor axonal delayed polyneuropathy or motor neuronopathy.

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