Original Article

A Study of Organophosphorus Induced Delayed Myelopathy: Uncommon Sequelae of a Common Poisoning

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Abstract

Introduction: Organophosphorus (OP) compounds, with their lipophilicity, are responsible for a spectrum comprising of acute cholinergic symptoms, intermediate syndrome, as well as delayed neurological sequelae in the form of OP-induced delayed neuropathy and subsequently, myeloneuropathy with predominantly thoracic cord affection, manifested on partial recovery of the neuropathy. The pathogenesis of this myeloneuropathy in humans is still not well perceived. **Aim of Study:** To determine the onset and course of development of delayed myeloneuropathy in patients of OP poisoning. **Materials and Methods:** Twelve patients of OP ingestion presenting with delayed myeloneuropathy were evaluated with prior history, examination, MR imaging, nerve conduction and electromyography studies, and various evoked potentials to elicit the pattern of disease manifestation and progression. **Results:** Among the included patients, a majority had consumed chlorpyrifos and permethrin composition, a majority had undergone gastric lavage. Five (41.7%) had experienced acute worsening and 8 (66.7%) patients had developed intermediate syndrome. OPIDN had appeared after a median of 4 (1–8) weeks after the poisoning. All patients had lower limb hypertonia with wasting and distal more than proximal weakness with pure motor or sensorimotor involvement. MRI showed thoracic cord atrophy in 3 (25%) patients. Motor-evoked potential with reduced amplitude was noted in lower limbs on lumbar stimulation but absent on cortical stimulation. **Conclusion:** Various animal models have shown similar patterns of neurotoxicity in OP poisoning with predominant thoracic cord pathology. Further research in humans may be undertaken to elicit the pathogenesis, thereby improving the treatment modality.

Keywords: Axonal neuropathy, diffusion tensor imaging, motor evoked potential, myeloneuropathy, thoracic myelopathy

Introduction

Organophosphorus compounds are chemicals with widespread uses as pesticides, industrial fluids, flame retardants, therapeutics, and nerve gas agents. They are derivatives of phosphoric (H_3PO_4), phosphorus or phosphonic (H_3PO_3), and phosphinic (H_3PO_2) acids. The electrophilicity of the phosphorus atom and the enhanced lipid solubility provides easy access to these molecules to cross the blood-brain barrier and produce neurotoxicity.[1] Organophosphorus (OP) insecticides cause three clinically distinct classical disease entities. In order of appearance after exposure these are 1) the acute cholinergic syndrome 2) the intermediate syndrome (IMS) and 3) OP-induced delayed polyneuropathy (OPIDP).[2-7] Neurobehavioral abnormalities in the form of drowsiness, confusion, lethargy, anxiety, emotional lability, and depression have also been described in certain studies under the constellation of chronic organophosphate-induced neuropsychiatric disorder (COPIND).[2] However, OPIDP comprising motor-predominant symmetrical lower limb polyneuropathy serves as a gateway unmasking the delayed central nervous system (CNS) involvement in the form of myelopathy which becomes evident as OPIDP recovers. This is a lesser explored entity and lacks adequate literature as to the pathophysiology of cord injury as well as the course of disease progression. In this study, a cohort of twelve patients with OP-induced myeloneuropathy was evaluated and thereafter discussed subsequently.

Aim of the Study

This study aims to evaluate the onset and progression of neurological events leading to delayed myeloneuropathy in cases of OP poisoning.

Materials and Methods

This is a tertiary hospital-based, single-centered, observational, cross-sectional, ambispective study. Twelve patients who presented to the hospital outpatient department within a period of two years (February 2020–February 2022) with a history of OP poisoning and the current status of subsequent myeloneuropathy were recruited in the study, irrespective of the duration of the disease. Five patients were recruited retrospectively and seven patients were recruited prospectively.

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On presentation, the relevant details of the acute poisoning and current clinical examination were done. Routine blood counts and biochemical parameters were recorded. Depending on the clinical assessment regarding the level of cord lesion magnetic resonance imaging (MRI), of spine with specific dedicated sections was done and assessed for any lesion. A cerebrospinal fluid (CSF) study was done to rule out other non-degenerative etiologies. For all patients, an autoimmune, demyelinating, vasculitis panel was evaluated to rule out other causes of myeloneuropathy. Serum vitamin B12 levels were recorded and any other deficiency or toxin induced disorders was negated. Nerve conduction study (NCS), electromyography (EMG) of affected muscle groups, electrophysiological (EP) studies, including visual evoked potential (VEP), tibial somatosensory evoked potential (SSEP) and motor evoked potential (MEP) were conducted in selected patients.

Results

Of the 12 patients with OP-induced delayed myeloneuropathy included in the study, their mean age was 31.42 ± 9.66 (range 20–52) years and only one patient was female. Among the patients, chlorpyrifos was consumed by 3, chlorpyrifos and permethrin by 4 and toxin composition was not known in 5 patients. In one patient toxin was consumed with alcohol. The median volume of toxin consumed was 150 (50–400) ml, gastric lavage was received by 8 patients and the median time to gastric lavage was 180 (30–360) min. Five (41.7%) patients had experienced immediate worsening ranging from aspiration pneumonia to acute respiratory distress syndrome and encephalopathy. The intermediate syndrome was observed in 8 (66.7%) patients seen at median days of 6 (3–14). Mechanical ventilation was done in 5 (41.7%) and the median ventilatory stay was 10 (2–30) days. OPIDN appeared after a median of 4 (1–8) weeks after the poisoning and presented to our institute after a mean of 32.33 ± 36.98 (range 1–120) months. One patient had an acute encephalopathy post-poison intake [Table 1].

All the patients had features of myeloneuropathy on presentation. CSF study was normal in all patients with a mean cell count of 2, all mononuclear varieties, and mean protein was 24.0 ± 2.65 mg/dl. On examination, all the patients had lower limb involvement with increased tone, wasting, and distal more than proximal pure motor or sensorimotor weakness. Deep tendon reflexes were brisk in the knee and absent in the ankles. Upper limbs were typically spared in all except 1 patient (pt#3) who had hypotonia and wasting of hand and forearm extensors [Table 2]. Routine complete blood count, liver and renal function tests, thyroid profile, and electrolytes

Table 1: Demographic profile of the patients

Case no.	Age/ gender	Type of poison/ amount	Gastric lavage	Immediate complications	Intermediate syndrome	Mechanical ventilation	Opidn onset	Presentation to our institute
1	24/M	Chlorpyrifos (50%) 400 ml	At 30 mins	Chest congestion at 36 hours	After five days of ingestion	For seven days developed post-intubation tracheal stenosis at one month	One month	Three months
2	29/M	Unknown	Unknown	None	None	None	One month	Twelve months
3	20/M	Chlorpyrifos (50%) + cypermethrin (5%) 250 ml	Not given	Acute respiratory failure	After seven days	For 20 days	One month	Eight months
4	26/M	Unknown	Unknown	None	None	None	One month	Three years
5	26/F	Chlorpyrifos 20% 100 ml	At 4 hours	Aspiration pneumonia	After seven days	For 10 days	two months	Six years
6	20/M	Unknown 200 ml	Not given	None	None	None	Three weeks	Four years
7	52/M	Unknown	At 2 h	None	None	None	Six weeks	Two years
8	35/MB	Chlorpyrifos + permethrin 50 ml	Not given	None	After 10 days	None	One month	Five years
9	40/M	Chlorpyrifos + Permethrin 200 ml	At 4 h	Acute onset encephalopathy since day 2	Couldn't be assessed	For one month	Four weeks	Two months
10	32/M	Chlorpyrifos+ cypermethrin 100 ml of alcohol	At 2 h	Acute respiratory distress	After five days	For two days	One week	One month
11	30/M	Unknown 50 ml	Not done	None	After three days	None	Four weeks	Two months
12	43/M	Chlorpyrifos 150 ml	At 6 h	None	After two weeks	None	Two weeks	Ten years

Table 2: Neurological examination of the patients

Cases	Muscle bulk	Tone	Power	Reflexes	Sensory	Posterior column	Autonomic features
1	Normal	Normal	UL proximal and distal 5/5 LL proximal 4/5 distal 2/5	B/L knee and ankle jerks diminished, UL normal	Normal	Normal	Normal
2	normal	Normal B/L UL Increased B/L LL	UL proximal and distal 5/5, LL around hip flexor 3/5, extensor and abductor 4/5, dorsiflexors 0/5, plantar flexors 2/5	B/L knee and ankle jerk brisk, UL normal	B/L distal LL 30%–40% loss of pain touch temperature	B/L JPS impaired, vibration sense impaired up to tibial tuberosity	Normal
3	Atrophy of B/L thenar, hypothenar, extensor compartment of the forearm, thigh, and anterolateral compartment of the leg	Hypotonia across B/L wrist joint and Lower limb across all joints	B/L UL proximal 5/5, Across wrist joint flexion 3/5, extension 2/5. B/L LL across hip joint 2/5, Knee joint 1/5, Ankle joint dorsiflexion 1/5, Plantarflexion 2/5. Truncal power 3/5	B/L upper limb diminished. B/L lower limb absent	L2 to S4 sensory loss 20%–30%	B/L JPS impaired in the great toe. Vibration sense absent below tibial tuberosity	LMN Bladder
4	None	Spasticity in all 4 limbs LL>UL	B/L UL proximal and distal 4/5, LL proximal 3/5, distal 2/5	Brisk in all four limbs	Normal	Normal	Normal
5	None	Normal B/L UL Increased across B/L hip joint Decreased across B/L ankle joint	UL proximal 5/5, distal 4/5, LL proximal 4−/5, Distal dorsiflexor 2/5, Plantar flexor 4−/5. Neck flexor 4−/5, extensor 4+/5.	B/L absent supinator jerk, Diminished bilateral knee and ankle jerk	Graded pain and temperature loss below hip 30% and knee 50%	B/L JPS impaired at the great toe	Normal
6	Wasting of bilateral lower limbs distal more than proximal	Normal B/L UL, Increased B/L LL	Upper limb proximal and distal 5/5. Lower limb proximal 4/5 across the hip. Distal dorsiflexor 3/5, Plantar flexor 4−/5.	Normal B/L upper limbs, Brisk B/L lower limbs.	B/L below ankle 40% decrease in pain touch temperature	B/L JPS impaired at the great toe	Normal
7	Normal	Normal B/L UL, Increased B/L LL	UL 5/5, LL proximal 4−/5, distal 4+/5.	Normal B/L UL. Brisk B/L LL	20% loss below knee bilateral symmetrical	B/L JPS impaired	Normal
8	Atrophy of bilateral distal lower limb anterior compartment predominantly	Normal in UL, Increased in LL	UL 5/5, LL proximal 4+/5, Distal Dorsiflexor 3/5, Plantarflexor 4−/5.	Brisk B/L knee, Reduced B/L ankles	30% loss below the knees bilateral	B/L JPS normal	Normal
9	Normal	Increased tone B/L LL	UL 5/5. LL proximal 5/5, distal 4−/5.	Brisk knee, Reduced ankle reflex.	20%–30% loss below the ankle	B/l JPS impaired	Normal
10	Normal	Increased B/L LL	UL 5/5. LL proximal 3/5, Distal dorsiflexion 2/5, Plantarflexion 2/5	Brisk knee, Reduced ankle reflex	Normal	Normal	Normal
11	Normal	Increased proximally B/L lower limb, distally normal	Power B/L LL Proximal 5/5, distal 4+/5.	Brisk knee and normal ankle reflex	Normal	Normal	Normal
12	Normal	Increased B/L LL	Power normal B/L UL. B/L LL proximal 4−/5, distal 3/5 dorsiflexion, 4−/5 plantarflexion.	Brisk knee and ankle reflex	Normal	Normal	Normal

UL = upper limb, LL = lower limb, B/L = bilateral

were in the normal range and serum connective tissue disease markers, the vasculitic and demyelinating panel were negative for all patients.

MRI showed predominantly thoracic cord atrophy in three (25%) patients with normal imaging in the rest. Diffusion tensor imaging of the spine at the lower thoracic level was done in three patients without cord atrophy to look for Wallerian degeneration. It did not show any significant change compared to the healthy controls in terms of the fractional anisotropy or apparent diffusion coefficient. Nerve conduction study showed mixed or motor predominant axonal polyneuropathy in bilateral lower limbs and electromyography was suggestive of neurogenic changes in distal more than proximal muscles of bilateral lower limbs. Tibial somatosensory evoked potential (SSEP) showed prolonged central motor conduction time (CSCT) in 3 patients (25%) with normal findings in rest. Motor-evoked potential (MEP) was evaluated in all four limbs in 4 patients (33.3%) by transcranial magnetic stimulation of the eloquent motor cortex. While upper limb MEPs were elicited on cortical stimulation, lower limb MEPs were elicited only on spinal stimulation with a reduced amplitude [Table 3].

Table 3: Investigation findings of the patients

Cases	Imaging	NCS finding	EMG finding	EP study
1	MRI spine normal	B/L upper limbs normal CMAP, B/L lower limb CMAP non-recordable. B/L SNAPS normal	EMG no spontaneous activity, low volitional MUAPs in bilateral TA and gastrocnemius	Not done
2	MRI spine shows cord atrophy at the lower cervical and upper thoracic level	Bilateral upper limbs normal CMAP. B/L lower limb motor axonal neuropathy reduced CMAPS, B/L SNAPs normal	EMG neurogenic MUAP in bilateral lower limbs no spontaneous activity	VEP and SSEP B/L normal study
3	MRI of spine and brain normal	All CMAPs absent B/L upper and lower limbs. All SNAPs normal	EMG spontaneous activity in FDI, EIP, VL, TA, Gastro cnemius. Distal muscles neurogenic MUAP.	B/L VEP, BAER study normal
4	MRI spine shows atrophy of the cord at the upper dorsal level	Asymmetric motor axonal type proximal more than distal polyneuropathy both lower limbs. Upper limbs normal. All SNAPs normal.	EMG shows spontaneous activity with neurogenic MUAP B/L lower limbs	B/L VEP and SSEP study normal
5	MRI spine with DTI normal	Asymmetric axonal motor and sensory lower limb > upper limb polyneuropathy	EMG lower limbs chronic neurogenic MUAPs without any spontaneous activity	VEP normal study B/L SSEP CSCT prolonged
6	MRI spine with DTI normal	b/l lower limbs symmetrical motor axonal neuropathy, upper limb normal, B/L SNAPs normal.	EMG reduced recruitment pattern b/l lower limb, s/o central inactivation	VEP and SSEP study normal
7	MRI spine normal	Normal study of all 4 limbs.	Not done	VEP and SSEP study normal
8	MRI spine shows cord atrophy at the lower thoracic level	b/l lower limb symmetrical sensorimotor axonal neuropathy	EMG lower limbs show a chronic neurogenic pattern without any spontaneous activity	VEP normal, B/L CSCT prolonged MEP shows an absence of bilateral lower limb potential on cortical stimulation, but generated potential on lumbar stimulation
9	MRI of brain and spine normal	B/l lower limb sensorimotor axonal polyneuropathy.	Chronic neurogenic changes B/L lower limbs.	SSEP normal
10	MRI spine normal	Motor axonal symmetrical polyneuropathy b/l lower limb	B/L lower limb chronic neurogenic MUAP, No spontaneous activity	VEP and SSEP study normal. Absence of b/l lower limb MEP on cortical stimulation, generated on lumbar stimulation.
11	MRI spine normal	Normal all four limbs	Normal all four limbs	VEP and SSEP normal. MEP was not generated on cortical stimulation, generated on lumbar stimulation.
12	MRI spine with DTI normal	Left > right asymmetric motor axonal polyneuropathy in both lower limbs	B/L lower limb chronic neurogenic MUAP, No spontaneous activity	Right CSCT prolonged VEP normal MEP not generated on B/L cortical stimulation

MRI = magnetic resonance imaging, B/L = bilateral, NCS = nerve conduction study, EMG = electromyography, EP = evoked potential, CMAP = compound muscle action potential, SNAP = sensory nerve action potential, MUAP = motor unit action potential, VEP = visual evoked potential, SSEP = somatosensory evoked potential, CSCT = central sensory conduction time, MEP = motor evoked potential, BAER = brainstem auditory evoked response

Discussion

OPs react covalently as pseudo-substrates at the catalytic center of a variety of serine hydrolases, including neuropathy target esterase (NTE) and acetylcholine esterase (AChE). In contrast to true substrates, the rate of hydrolysis of the phosphorylated enzymes is extremely slow. A second reaction of aging occurs concurrently, exclusively in OP compounds, resulting in cleavage of one of the bound alkyl groups of the phosphoryl residue, thus permanently damaging the enzyme. NTE is thought to be involved in membrane trafficking and lipid homeostasis required for the maintenance of axons.[6]

OPs with slow pharmacokinetics or at relatively lower doses may cause OPIDP after a lag time of 4–5 weeks, whereas higher doses of OPs may reduce this period to as little as 10 days.[6] Four distinct stages of OPIDP are known. The initial phase 1, latent period, varies from 1 to 3 weeks of exposure and depends on the route of administration, type and amount of poison ingestion, and individual metabolic parameters.[8] The second progressive phase consists of motor-sensory neuropathy in the form of foot drop with associated glove stocking pattern of sensory loss or positive sensory phenomenon.[8] The third stationary phase brings a stabilization of the disease course. The final phase of improvement causes the disappearance of sensory symptoms in a craniocaudal manner followed by a partial recovery in motor power following which pyramidal and other signs of central neurologic involvement become more evident.[8] All our patients recruited were in the late third to the fourth phase of their disease course.

Neurophysiological findings of OPIDN are normal sensory NCS, normal or minimally abnormal motor NCS, prolonged distal latencies, reduced amplitude of CMAP, delayed terminal motor latencies, and slightly reduced motor NCS.[9] Our patients presented a mixed pattern on NCS with both symmetric and asymmetric axonal patterns of motor predominant polyneuropathy with a few having normal studies. Electromyography reveals signs of denervation of the affected muscles with increased insertional activity, spontaneous activity (fibrillation potentials and positive sharp waves), and reduced interference pattern. During recovery, polyphasic motor unit potential (MUAP) appears.[6] This is in concurrence with our patients' parameters where chronic denervation pattern was seen with polyphasic MUAPs.

The pathophysiology of predominant lower limb involvement with myeloneuropathy can be explained by the animal models of Read *et al.*[10] The association of increased neural phosphatidylcholine (PtdCho) in OP-dosed mice with degeneration confined to the longest spinal axons with an increasing area of axonal damage suggests a linkage between neural PtdCho homeostasis and axonal maintenance.[10] On examining the lumbar spinal cord few lesions were observed in axons of the dorsal tract and numerous degenerating axonal lesions in the corticospinal tract displayed a Wallerian-like morphology. In older mice, swollen axons with disorganization were increasingly present in lumbar tracts.[10] These mechanisms are strikingly similar to the pathogenesis of hereditary spastic paraparesis (HSP) in which distal parts of the longest spinal axons are damaged earlier in both spastin and NTE-deficient mice. In a postmortem study by Deluca *et al.*[11] reported maximum reduction in CST nerve fiber density was in the upper thoracic (51%), CST column area reduction in the upper thoracic (41%) and lower thoracic (42%), change in total axon number upper thoracic (69%) and lower thoracic (61%) levels in HSP patients compared to controls which explain the predominant thoracic cord atrophy in OP myelopathy. This is the possible mechanism of OP myelopathy predominantly affecting the upper or lower thoracic cord sharing the same semiology as HSP as evident in our patients coinciding with prior literature.

Senanayake *et al.*[12] has described a cohort of 20 Indian Tamil girls with tri-cresyl poisoning followed up for three years amongst whom 50% developed mild pyramidal involvement by end of one year and recovered completely by end of 3 years. OP induced myelopathy however has worse disease course as evident in our patients with the majority sustaining the same disability score as that during the presentation to us or showing minimal improvement. Nayak *et al.*,[8] in their study, also described three patients of OP myelopathy with a similar presentation as our patients. Agarwal *et al.*[13] described a patient of acute encephalopathy followed by delayed OP-induced myelopathy in chlorpyriphos poisoning with normal imaging parameters similar to one of our patients. Merwin *et al.* have also suggested OP as a possible candidate neurotoxin in the development of amyotrophic lateral sclerosis.[14]

Conclusion

OP-induced myelopathy is a rare but important clinical entity that deals with the aftermath of acute poisoning. Further research in aspects of the pathogenesis and imaging parameters are required to strengthen our current understanding of the disease mechanism.

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Conflicts of Interest

There are no conflicts of interest.

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