Case Report

Cholinergic crisis, intermediate syndrome and delayed polyneuropathy following malathion poisoning

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Abstract. Organophosphate poisoning is common in developing countries, more so in India. A 7-year-old boy with history of ingestion of unquantified amounts of malathion, presented to the pediatric emergency of Calcutta National Medical College, Kolkata in acute cholinergic crisis. He was treated with atropine and pralidoxime. The acute cholinergic crisis persisted for four days after admission, and as it subsided, the child developed respiratory distress, bulbar palsy, cyanosis, hypoxemia and hypercarbia. A diagnosis of intermediate syndrome was made and patient needed prolonged ventilation for 21 days for type II respiratory failure. Five days after discharge, the child developed distal weakness of both lower limbs, which later involved the hands. There was associated gross sensory loss. Nerve conduction velocity study and sural nerve biopsy predominantly showed evidence of sensory-motor axonopathy with associated demyelination. The child was treated with physiotherapy, but was left with disabilities like claw hand, foot drop and the inability to walk.

Keywords: Organophosphorus poisoning, cholinergic crisis, intermediate syndrome, organophosphate induced delayed neuropathy, malathion, acetylcholinesterase

1. Introduction

According to the World Health Organization, an estimated three million cases of organophosphorus (OP) poisoning with two thousand deaths occur per year [1]. In the neuromuscular junction, acetylcholine is released when a nerve impulse reaches the terminal axonal end.

The enzyme acetylcholinesterase (AChE) splits acetylcholine into acetic acid and choline [2]. In OP poisoning, the cholinesterase enzyme is phosphorylated resulting in accumulation of excess acetylcholine with ensuing systemic effects [2]. Following OP poisoning, the clinical features can be categorized in table 1 [2–6].

2. Case report

A 7-year-old boy from Baruipur, India, son of a farmer, had accidentally consumed unquantified amounts

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Table 1
Clinical features of organophosphate poisoning

Acute symptoms	Intermediate syndrome	Organophosphate induced delayed neuropathy
<p>Muscarinic syndrome</p> <p>Occurs due to excessive stimulation of muscarinic receptors.</p> <p>Manifested by bradycardia, hypotension, bronchospasm, hypersalivation, conjunctival hyperemia, miosis, and diaphoresis.</p> <p>Central nervous system syndrome</p> <p>Occurs with organophosphorus compounds that cross the blood brain barrier.</p> <p>Manifested by anxiety, ataxia, tremor, seizures, depression of mental status and central respiratory drive [2].</p> <p>Autonomic manifestations include hypertension, tachycardia, mydriasis and pallor [23].</p> <p>Acute symptoms occur immediately after exposure and the duration depends on the severity of intoxication [2].</p>	<p>Clinical features occur 24–96 h after poisoning.</p> <p>Incidence is 8–49%.</p> <p>Occurs due to down regulation of pre and post-synaptic nicotinic receptors resulting in release of excessive acetylcholine and calcium ions respectively [3].</p> <p>Initial manifestations are muscle fasciculations and cramping, later followed by acute muscular paralysis involving neck flexors, proximal limb and respiratory muscles and even cranial nerves innervated muscles. Distal muscles are relatively spared [3].</p> <p>Complete recovery occurs within 5–18 d [3].</p>	<p>Occur subacutely 2–4 wk after poisoning [2].</p> <p>A predominantly motor neuropathy initially involving the distal leg muscles followed by the small muscles of the hand. Later there may be proximal extension resulting in truncal weakness.</p> <p>Myelopathy with involvement of the corticospinal tracts and the dorsal column, predominantly of the thoracic spine, may also occur due to liposolubility of these substances [4,5].</p> <p>Pathogenesis is phosphorylation and ageing of the enzyme neurotoxic esterase resulting in stoppage of axonal flow, thereby causing long axonal degeneration, loss of myelin and macrophage accumulation [6].</p>

of malathion (diethyl 2-[(dimethoxyphosphorothioyl) sulfanyl] butanedioate), that was stored in their house to be used as a pesticide. He presented in the pediatric emergency with features of cholinergic crisis, excessive salivation, lacrimation, rhinorrhoea, sweating and recurrent vomiting. Glasgow coma scale score was 6/15, conjunctiva was hyperemic, pinpoint pupils, bilateral crackles and rhonchi over all lung fields, and pulse rate was 60/min, respiratory rate 14/min, blood pressure 80/50 mmHg. The patient was admitted in pediatric intensive care unit and immediate gastric lavage was done. He was treated with injection atropine 0.05 mg/kg intravenously every 10 minutes for two hours and then continuous infusion at 0.08 mg/kg/h. Pralidoxime (2-pyridine aldozimemethiodide) 50 mg/kg bolus dose followed by continuous infusion of 15 mg/kg/h was started. To maintain normal oxygen saturation, free flow oxygen 6 L/min was given by facemask. Investigations revealed leucocytosis ($14,200/\text{mm}^3$) with neutrophilia (74%). However, other hematologic and biochemical parameters (renal, liver function tests, electrolytes) were

normal. Chest X-ray showed ill-defined opacities. Erythrocyte cholinesterase level (sent before oxime therapy) was $2000 \mu\text{mol/mL/min}$ by Ellman technique using Model 460 AChE Assay Kit manufactured by EQM Research Incorporate, USA (Reference range $5000\text{--}9000 \mu\text{mol/mL/min}$) [7]. The features of cholinergic crisis improved significantly with treatment. Hence, atropine and pralidoxime infusions were tapered and stopped four days after hospital admission.

As he was being planned to be shifted to the general ward, he developed respiratory distress, cyanosis, paradoxical respiration, head drop, dysphagia, pooling of secretions in pharynx, nasal intonation of speech, dysarthria and loss of gag reflex. Arterial blood gas study revealed pH 7.1, partial pressure of oxygen was 45 mmHg, partial pressure of carbon dioxide was 60 mmHg and bicarbonate was 26 mEq/L, thereby signifying carbon dioxide retention (type II respiratory failure). He was immediately intubated and mechanically ventilated. His electromyography revealed significant decrement on fast frequency (30 Hz) repetitive

nerve stimulation test, consistent with neuromuscular junction disorder secondary to OP poisoning, hence a diagnosis of intermediate syndrome was made. However, a single electrical stimulation did not invoke repetitive response. Magnetic resonance imaging of brain and cerebrospinal fluid examination following lumbar puncture were normal. Serum creatine phosphokinase was 200 U/L (reference value <118 U/L) and lactate dehydrogenase was 550 U/L (reference range 225–450 U/L). Ventilation and supportive management with intravenous fluids, empirical antibiotics (ceftriaxone at 75 mg/kg/d and cloxacillin at 100 mg/kg/d), nutritional support, and postural care were continued. Repeated attempts to wean the child from ventilation failed due to persistent respiratory muscle weakness. Recovery of muscle power started in the cranial nerve innervated muscles from the 18th day of ventilation, followed by recovery of the respiratory muscles and the child could be extubated after 21 days. After a stay of 26 days in pediatric intensive care unit, he was shifted to the general pediatric ward. Initially he had slight weakness (grade 4/5 power) in proximal muscles of lower limbs. This weakness recovered within five days and he could walk without support and perform all activities of daily living independently at discharge 30 days after hospital admission. Thus, the child had complete recovery from intermediate syndrome.

He returned within five days with complaints of tingling sensations in both feet and difficulty walking. Meanwhile, he also developed tingling sensations and weakness in the grip of both hands. Preceding the onset of weakness, there was no history of fever, gastrointestinal or respiratory infections and vaccination. On examination, the child was found to have normal cognition, no cranial neuropathies, wasting and hypotonia of thenar and hypothenar eminences, calf and peroneal

muscles of lower limbs. Evertor, invertor, dorsiflexor and plantiflexors of the ankle joints had grade 1/5 power. Small muscles of the hand (thenar, hypothenar muscles, lumbricals, dorsal and palmar interossei) were significantly weak. Muscles acting on knee and hip joint were normal. Ankle and supinator jerks were lost, but other deep tendon jerks were normal; bilaterally plantar reflexes were unresponsive. There was positive Romberg sign and high stepping gait due to foot drop. All modalities of sensation below the ankle and wrist joints were grossly diminished. There was no bladder or bowel involvement, dysautonomia and thickening of peripheral nerves. The weakness was progressive and the child was unable to walk within two weeks. Nerve conduction study (Table 2) revealed grossly reduced compound muscle action potential amplitudes and conduction velocities in bilateral tibial and right peroneal nerves. Left peroneal, bilateral median and ulnar nerves were unexcitable. Sensory nerve action potentials of bilateral sural nerves were nonrecordable. Thus, there was gross distal sensory-motor axonopathy with features of demyelination too. Needle electromyography demonstrated increased insertional activity and fibrillation potential. Sural nerve biopsy showed axonal degeneration and demyelination. Thoracolumbosacral magnetic resonance imaging and repeat cerebrospinal fluid study was normal.

Neuropathic pain and paresthesia improved with carbamazepine (15 mg/kg/d). Ankle-foot orthoses was given and physiotherapy was started. On follow up over the next four months, there was no further proximal progression of the weakness and no appearance of upper motor neuron signs. However, recovery of motor function was minimal and the child was left with deformities like claw hand, foot drop and the inability to walk. Follow up nerve conduction velocity study after two months showed results similar to the initial study.

Table 2
Nerve conduction study showing conduction velocities, compound muscle action potential and sensory nerve action potentials amplitudes of upper and lower limb nerves

Motor nerve conduction velocity (m/sec)	Normal value [12]	Patient value
Tibial (right/left)	>48 / >48	31.5 / 31.3
Peroneal (right/left)	>44 / >44	32.4 / No response
Median (right/left)	>52 / >52	No response
Ulnar (right/left)	>50 / >50	No response
Compound muscle action potential amplitude (mV)	Normal value [12]	Patient value
Tibial (right/left)	>5 / >5	0.79 mV / 0.54 mV
Peroneal (right/left)	>2 / >2	0.46 mV / No response
Median and ulnar nerves	>4	No response
Sensory nerve action potential amplitude (μV)	Normal value [12]	Patient value
Sural nerve	>5	No response

3. Discussion

The child developed cholinergic crisis, intermediate syndrome and delayed neuropathy following severe malathion poisoning. During the period of cholinergic crisis, the child required a cumulative dose of 115 mg of atropine and 25 g of pralidoxime.

At the onset of intermediate syndrome, the signs of cholinergic crisis had abated. However, the continuum or relapse of cholinergic crisis at the onset of intermediate syndrome had also been reported [8,9]. In our case, there were severe features such as respiratory failure and bulbar palsy. Although intermediate syndrome resolves within 5–18 days, the reported child showed evidence of prolongation up to 21 days [10]. Prolonged intermediate syndrome with respiratory failure for 23 and 21 days in 23 year-old and 19-year-old patients respectively had been reported previously [11,12]. However, there was no cranial neuropathy in either case. Maximum duration of intermediate syndrome has been reported to be 30 days [13].

The hallmark of intermediate syndrome-decremental response at 30 Hz in repetitive nerve stimulation test was seen in our case. Other features have also been described like single supramaximal electrical stimulus induced repetitive response and decremental-incremental response to high frequency [2,14]. However, these findings were not found in our child.

Intermediate syndrome is usually associated with severe poisoning and inhibition of at least 80% of the synaptic AChE [15]. Poisoning with parathion (oxygen, oxygen-diethyl oxygen-[4-nitrophenyl] phosphorothioate), methylparathion, methamidophos (oxygen, sulfur-dimethyl phosphoramidothioate), monocrotophos (dimethyl [E]-1-methyl-2-[methylcarbamoyl]vinyl phosphate) and fenthion (oxygen, oxygen-dimethyl oxygen-[3-methyl-4-(methylsulfanyl)phenyl] phosphorothioate) are often associated with intermediate syndrome [11,15]. Malathion poisoning has also been reported to cause intermediate syndrome by Azazh [12]. Although inadequate dose of oximes is postulated as a cause of intermediate syndrome [16], it developed in our case despite adequate pralidoxime therapy possibly because of the fact that dimethylphosphorylated AChE (a compound formed in malathion poisoning) has a very short aging half life and not susceptible to the reactivation action of oximes for longer periods [17]. However, few reports indicate that intermediate syndrome and delayed effects of OP poisoning are not influenced by atropine and oxime therapy [18].

Elevated creatine phosphokinase and lactate dehydrogenase levels during intermediate syndrome indicate some degree of myonecrosis due to excessive calcium ions mobilization within muscle fibers. The possible role of this muscle injury has also been implicated in the development of intermediate syndrome [19].

Organophosphate induced delayed neuropathy (OPIDN) is a rare cause of peripheral neuropathy [20]. Although OPIDN is principally a motor axonopathy, our child revealed severe affection of both motor and sensory components. Sensory affection in OPIDN, although to a lesser degree than motor affection has also been reported by few authors [21,22]. The youngest case of peripheral neuropathy following OP poisoning was reported in an 8-year-old boy [23]. Even on a 12-month follow up, there was no proximal extension of the weakness or appearance of signs of myelopathy. However, a regular follow-up was advised since delayed onset of myelopathy 18-months after poisoning have been reported [5] and in Senanayake et al. [10] nearly 50% of patients had some evidence of pyramidal tract dysfunction.

Clinical features of OP poisoning appear when erythrocyte cholinesterase activity is <75% of normal and muscle paralysis occurs at levels <20% [2,12]. In our case, severe manifestations occurred despite the cholinesterase level being 40% of normal. This could be attributed to the higher susceptibility of children to OP pesticides due to lower levels of paraoxonase I (enzyme needed to detoxify OP compounds) compared to adults [24]. In addition, the peculiar property of malathion can be attributed to this phenomenon. Malathion, when stored over long periods, can produce by-products that inhibit the liver enzymes responsible for its degradation, thus enhancing its toxicity [25]. Liver microsomes convert thions (phosphorus=sulfur) to oxons (phosphorus=oxygen) i.e. malaaxon, which is more toxic [26].

In conclusion, it needs to be emphasized that in India, there are very few case reports documenting neurotoxicity of OP compounds and all were following dichlorovas poisoning [3]. Nand et al. [3] and Azazh [12] reported all three syndromes in succession in 19-year-old men following chlorpyrifos and malathion ingestion respectively. However, the much younger age of our case (7 years old), cranial neuropathy during intermediate syndrome, and presence of severe sensory neuropathy and absence of features of myelopathy differentiated our case from the above-mentioned cases.

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