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Case Series

Delayed neurological complication of organophosphate intoxication

Shubham Aryan[1]*, Kirti[2], Sumit Kumar[1], Chavi Sharma[1], Naveen Rao[1], Himanshu Lata[3]

[1]Department of Medicine, GGSMCH Faridkot, Punjab, India
[2]Department of Biochemistry, GGSMCH Faridkot, Punjab, India
[3]Department of Obstetrics and Gynaecology, GMC Amritsar, Punjab, India

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***Correspondence:**
Dr. Shubham Aryan,
E-mail: aryanshubham193@gmail.com

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ABSTRACT

Organophosphate are one of the most commonly used pesticide in India and across the global, because of easy accessibility it is often misused as homicidal and suicidal cases that carry high rate of mortality and morbidity. It often affects the body by acting on synaptic cleft and interfere acetylcholine present inside the clefts. Early manifestation includes the increased secretion across the body with decrease heart rate. Here we had a case series of patients presented with delayed neurological complication of organophosphorus compounds (OPC).

Keywords: Organophosphate, OPC compounds, Pesticide, Poisoning

INTRODUCTION

Acute poisoning is one of the major causes of morbidity and mortality worldwide, with 90% of the burden of fatal poisoning coming from developing countries. In developed countries, the rate of mortality from poisoning is 1-2%, but in India, it varies around 20%.[1,2] Poisoning is a major epidemic of non-communicable diseases in the present century. Among the unnatural deaths, deaths due to poisoning come next only to road traffic accident deaths. In earlier times, the poisoning deaths from pesticides were mainly accidental but easy availability, low cost, and unrestricted sale have led to an increase in suicidal and homicidal cases as well.[3] In developing countries, the widespread use of organophosphorus compounds (OPCs) has been accompanied by an appreciable increase in the incidence of poisoning with these agents, both suicidal and accidental. This is attributed mainly to their early availability, indiscriminate handling, storage, and lack of knowledge about the serious consequences of poisoning. Of the various substances used for suicidal attempts in India, OPCs form a significant group.[4] Clinical manifestation of OPC poisoning is diverse ranging from mild symptoms to fatal complications over time, we need proper management of the situation. OPC compounds, being highly lipid soluble, easily penetrate the skin and gastric mucosa and are thereby rapidly distributed to tissues and penetrate the blood-brain barrier to act on the CNS system.[5] The severity of poisoning depends upon the mode of ingestion, dose consumed, quality, and type of organophosphate exposure.[7] The key feature of organophosphate is their capacity to inhibit carboxyl ester hydrolases, primarily focusing on AChE inhibition. These insecticides inactivate AChE by phosphorylating the serine hydroxyl group on the enzyme. As AChE is essential in acetylcholine degradation, its inhibition results in an accumulation of acetylcholine within the synapse, resulting in excessive stimulation of both nicotinic and muscarinic receptors.[9] Organophosphate poisoning shows clinical symptoms in three phases. It first manifests as a cholinergic syndrome, the symptoms include miosis, nausea, vomiting, diarrhea, dyspnea, and bradycardia. Seizures, coma, and respiratory failure may also occur. Intermediate syndrome, which typically occurs 24-96

hours after an intensive cholinergic crisis, is characterized by acute ventilatory insufficiency due to the paralysis of the respiratory muscles. The intermediate syndrome is thought to result from a dysfunction of the neuromuscular junction, which occurs in association with the prolonged overstimulation of the cholinergic receptors. Finally, on rare occasions, delayed neuropathy develops at several weeks after exposure. Organophosphate-induced delayed neuropathy (OPIDN) is an axonal polyneuropathy that is characterized by distal weakness and sensory loss, which may be progressive and severe.[6] Type III paralysis or organophosphate-induced delayed neuropathy (OPIDN) is a pure motor or predominantly motor axonal neuropathy characterized by wrist drop and foot drop with minimal or no sensory loss which occurs 2-3 weeks after exposure to an OP agent. The pathogenesis of OPIDN is different and it is presumed to be due to the phosphorylation and aging of an enzyme in the axons called neurotoxic esterase or neuropathic target esterase (NTE). Inhibition of NTE causes degeneration of predominantly long axons, with loss of myelin and macrophage accumulation in nerves leading to motor axonal neuropathy. Sensory disturbances are usually mild. Delayed neurotoxicity primarily affects distal muscle groups, but in severe neurotoxicity, proximal muscle groups and the central nerves system were also affected may also be affected.[8] Here we have a case presented with delayed complication of OPC poisoning after 6 weeks.

CASE SERIES

Case 1

We had a 32-year-old male patient presented to the hospital with complaints of weakness of upper limb and lower limb for 15 days. Patient initially had difficulty in wearing the slipper and often had history of slipping of slippers, later over a period of 1 weak this weakness slowly increases such that patient was unable to bear the weight on bilateral lower limbs. Patient also had complaint of difficulty in gripping the objects, doing fine work and later this too increases such that patient was unable to wear his clothes and finally over a period of 15 days he was bed ridden though there is no history of difficulty in speech, swallowing, blurring of vision, diplopia, headache, vomiting. On examination patient was calm conscious and oriented to time place and person. Tone was decreased in b/l lower and upper limb.

Patient was admitted one month ago with alleged history of OPC poisoning and was treated for same with atropine and pam. Patient was discharged in haemodynamically stable state Later patient was stable and start doing his normal work for 5-6weeks but later patient start developing the numbness and weakness of lower limb that start from foot which later ascend to knee and thigh and within 1 week it involves upper limb an patient was bed-ridden. Our patient present with insidious onset progressive ascending paralysis with loss of speech, difficulty in swallowing, though patient attendant initially masks the history of OPC but later on scrutiny we found the low level of cholinesterase enzymes revealing the OPC poisoning that patient later admit. MRI was done that was non-significant and NCV done that show motor axonal neuropathy in upper limb and lower limb, that favors the diagnosis of OPIDN.

Table 1: Power at various joints.

Joint	Left	right
Shoulder	1+	1+
Elbow	1+	1+
Wrist	1+	1+
Hip	1+	1+
Knee	1+	1+
Ankle	1+	1+

Table 2 : Deep tendon reflexes.

Joint	Left	Right
Elbow	Absent	Absent
Supinator	Absent	Absent
Knee	Absent	Absent
ankle	Absent	Absent

Table 3: Investigations.

NCCT head	WNL
MRI brain with whole spine screening	WNL
Serum cholinesterase level	decreased
Nerve conduction study	Motor neuropathy

Case 2

A 22-year-old male presented to the hospital with complaints of bilateral upper limb and lower limb weakness 2 months. Patient initially had complaint of numbness of lower limb and upper limb. Patient start difficulty in griping the slippers that slowly progress over period on 15-20 days such that patient start difficulty in walking and often unable to weight on lower limb and similarly patient had start difficult in holding the object, difficulty in buttoning and unbuttoning and finally over 20 days was unable to wear shirt. The weakness ascends in such way that patient was bed ridden within 2 months and presented to us with quadriplegia. On examination the patient was calm conscious and oriented to time place and person. Tone in b/l upper limb and lower limb was increased.

All other investigation including NCCT head, MRI brain was with in normal limit though Serum cholinesterase level is decreased and NCV show motor neuropathy. 22-year-old male presented to the hospital with complaints of insidious onset gradually progressive ascending weakness associated with increased rigidity of limbs since 2 months. No history of waxing waning pattern, diurnal variation,

associated numbness or tingling sensation. No history of neck pain, heavyweight lifting, headache, fever, altered sensorium, blurring of vision. Patient had a past history of consumption of poison chloro (organophosphate) 1 month prior to this episode. Patient taken treatment for the same at private hospital, managed conservatively with atropine, pralidoxime, antibiotic, fluids and PPI. Hospital admission was uneventful, patient was vitally stable with routine investigation within normal limits with acetylcholinestrase level of 174 which is markedly reduced, and got discharged after 4 days. No history of DM/HTN/ thyroid disorder any exposure to heavy metal. Patient is calm conscious cooperative oriented to time place person. Vitals od the patient, BP-120/70 mmHg PR-78 per minute, SpO2-98 % on room air, temp 98.2 F.

On systemic examination HMF, language, speech, cranial nerve normal. Patient having high steepage gait with foot drop. On motor examination bulk bilateral equal with hypertonia, power in upper limb 4/5 across all joint bilaterally and in lower limb proximal 3/5 and distally 2/5, hyperreflexia with DTR 3+ clonus absent, plantars mute bilaterally. Sensory and cerebellum examination within normal limits. Routine blood investigation, TFT, HBA1c, Nerve conduction study, MR brain with cervical spine done. Nerve conduction study suggestive of pure motor polyneuropathy, bilateral tibial and peroneal nerve recorded no motor response, while motor response in right and left median and ulnar nerve are reduced, sensory functions are preserved. Rest all investigation were within normal limits. Repeat cholinesterase level were within normal limits. Patient managed conservatively with low dose steroid, methyl cobalamin, pregabalin, physiotherapy and vitamin E. On follow up after 2 weeks of therapy patient had improvement in his weakness.

Table 4: Power at various joints.

Joint	Left	Right
Shoulder	1+	1+
Elbow	1+	1+
Wrist	1+	1+
Hip	1+	1+
Knee	1+	1+
Ankle	1+	1+

Table 5: Deep tendon reflexes.

Joint	Left	Right
Elbow	3+	3+
Supinator	3+	3+
Knee	3+	3+
ankle	3+	3+

Case 3

A 25-year-old male presented to hospital with complaint of weakness of bilateral lower limb and difficulty in walk from past 1 month. Patient initially was unable to lift his foot from ground and often drag the foot while walking and later this progress to involve whole lower limb such that he was unable to bear the weight on both limb and often fall.

On examination the patient is calm conscious and oriented to time place and person. Tone in b/l upper limb was normal and lower limb was increased. All other investigation including NCCT head, MRI brain was with in normal limit though serum cholinesterase level is decreased and NCV show motor neuropathy. The gait analysis exhibited a spastic gait with a stiff knee and scissoring pattern accompanied with bilateral drop foot.

Table 6: Power at various joints.

Joint	Left	Right
Shoulder	5+	5+
Elbow	5+	5+
Wrist	5+	5+
Hip	2+	2+
Knee	2+	2+
Ankle	2+	2+

Table 7: Deep tendon reflex.

Joint	Left	Right
Elbow	2+	2+
Supinator	2+	2+
Knee	3+	3+
ankle	3+	3+

Case 4

31-year-old female with alleged history of OPC poisoning 4 weeks ago and presented with complaints of cramping calf pain and hyperesthesia in the plantar area followed by distal weakness in the lower limbs and, two days after, in the upper limbs.

Table 8: power at various joints.

Joint	Left	right
Shoulder	5+	5+
Elbow	5+	5+
Wrist	5+	5+
Hip	2+	2+
Knee	2+	2+
Ankle	2+	2+

Table 9: deep tendon reflexes.

Joint	Left	Right
Elbow	3+	3+
Supinator	3+	3+
Knee	3+	3+
ankle	3+	3+

On examination the patient is calm conscious and oriented to time place and person. Tone in b/l upper limb was normal and lower limb was increased. Sensory system examination show decrease in crude and fine touch bilaterally.

DISCUSSION

OPCs are commonly used as pesticides, lubricants and petroleum additives. They can enter the human body through absorption from the skin, by being ingested or inhaled. The primary site of OPC is neuromuscular junction where it acts mainly on Acetylcholinesterase (AChE) enzyme and therefore increase the level of acetylcholine at NMJ leading to overstimulation and various cholinergic and nicotinic manifestation. Unlike acute cholinergic syndrome and the intermediate syndrome, OPIDN is not directly related to cholinergic overstimulation. Previously, OPIDN has sometimes been reported as Guillain-Barré syndrome because of its rapid progression after a latent period and systemic involvement. However, the current consensus is that OPIDN is distinct from Guillain-Barré syndrome and is caused by the neurotoxicity of organophosphorus compounds. Electrophysiological examinations are important in the diagnosis of OPIDN for distinguishing it from the initial cholinergic crisis and intermediate symptom.[10]

Pharmacological treatment was started by using a loading dose of atropine and pralidoxime. Atropine is a tertiary amine which acts as a competitive antagonist of acetylcholine at the muscarinic postsynaptic membrane and in the CNS.11 The loading dose of atropine was 1.8 to 3 mg (3-5 vials) through intravenous route, then the dose was doubled every five minutes interval till target endpoint of atropinization (i.e., clear chest on auscultation, pulse>80 beats/minute, pupils no longer pinpoint, dry axilla and systolic BP>80 mm Hg). After achieving atropinization maintenance dose was started with 10 to 20% of the total dose of atropine needed for the patient to be atropized but not more than 30 mg approximately at 3–5 mg/hour. Then monitoring was done every 15 minutes interval to settle the infusion rate. During the infusion period if toxicity (i.e., confusion or delirium, pyrexia, absent bowel sounds or urinary incontinence) developed, atropine infusion was stopped and symptomatic management was started. Atropine infusion was restarted at 70-80% of the previous infusion rate after disappearance of signs of toxicity. In case of loss of atropinization (e.g., bronchospasm/bradycardia) a bolus dose of atropine was given and infusion rate was increased till the signs disappeared. After stabilization of all parameters, all cases were monitored hourly till required dose of atropine decreased, then cases were monitored 2-3 hourly and continued for 2-5 days. Tapering was done over 3rd to 5th day.[3] Current WHO guideline for pralidoxime therapy is as follows, 30 mg/kg over 10-20 minutes as loading dose followed by a continuous infusion of 8-10 mg/kg/hour until clinical recovery (after 12-24 hours atropine is no longer required or patient is extubated) or 7 days.[12]

Pralidoxime is a quaternary ammonium compound with poor CNS penetration which reactivates acetylcholine by removing the phosphoryl group from OP compound and causes recovery of neuromuscular transmission.[13] There is still no consensus on the management of OPIDN. Some prefer physiotherapy alone, but it may take up to 9 months to recover.[16] The hyperesthesia may be controlled by amitriptyline, carbamazepine and capsaicin. The use of thiamin is recommended by some authors but it has not been shown to alter the appearance of OPIDN.[17] It is also suggested that recovery or good prognosis will be expected with B1, B2, B6, B12 and methylprednisolone as long as they are given before paralysis develops in delayed neuropathy.14 It is due to phosphorylation and inhibition of an enzyme called Neuropathy Target Esterase (NTE), which is located within the nervous tissue. It catalyzes the breakdown of endoplasmic reticulum-membrane phosphatidylcholine and plays an important role in membrane-phospholipid homeostasis, axonal transport and glial-axonal interactions.[15] In Organophosphate poisoning, there is phosphorylation and subsequent aging of at least 70% of NTE in the peripheral nerves.[16]

CONCLUSION

Patient with OPC poisoning should be thoroughly followed up and if any kind of motor weakness or numbness occurred in patient the OPIDN should be kept in mind and should be ruled out.

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