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Case Report

ORGANO PHOSPHORUS COMPOUND POISONING, COMPLICATED ACUTE RENAL FAILURE AND DELAYED POST HYPOXIC ENCEPHALOPATHY - A CASE REPORT

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ABSTRACT

Organophosphorus compound (OPC) poisoning is one of the most common poisons in rural India. We present a 27year old female patient who came to us in altered sensorium and froathing from mouth with an alleged history of OPC intake about 2 hours back. The patient was intubated, connected to a mechanical ventilator and atropinized. On day 3 of admission patient had elevated renal parameters and was diagnosed as Acute Renal Failure due to acute tubular necrosis probably poison induced. On day 4 of admission she suffered an acute cardiac arrest and was resuscitated; following this she gradually improved and after 3weeks of intensive management her sensorium deteriorated. MRI Brain showed Diffuse Cerebral White Matter Leukodystrophy due to DEMYELINATION (Hypoxia induced).

KEYWORDS: Organophosphorus compound poisoning, Acute renal failure, demyelination, leukoencephalopathy.

INTRODUCTION

Organophosphorus compound (opc) poisoning is very common owing to its easy availability and accessibility in rural India. It claims many a lives and the rest move on with morbidities of prolonged hospitalization and ventilator support. Mortality most often is attributable to respiratory failure, while others succumb to complications like convulsions, hepatic dysfunction, pancreatitis, pyrexia, intermediate syndrome (IMS), and delayed syndrome.[1,2] Most of these however depend on type of compound, concentration, amount and time of intervention of treatment after consumption. This case report deals with a rare presentation of ARF and hypoxia induced demyelination leading to diffuse cerebral white matter leukodystrophy in a patient of opc poisoning.

CASE REPORT

A 27year old lady was brought to our hospital casualty with alleged history organophosphorus compound poisoning (monochrotophus), exact quantity not known (as history was obtained from patient attenders). We received her in altered sensorium with breathlessness, sweating and froathy secretion from the mouth.

On examination patient was unconscious, had fasciulations, bilateral pupils pin point, diaphoresis present, smell of kerosene present in breadthe, pulse-120/min, BP- 100/60 mm Hg, Cvs- S1S2present, Rs- SpO2-80% in room air and bilateral coarse crepitations present, P/A- soft and CNS- comatosed, moving all limbs, reflexes diminished and plantar extensor.

In view of respiratory distress the patient was intubated with 7.5' endotracheal tube and connected to mechanical ventilator (volume control mode). Inj.atropine 6mg i.v stat dose given followed by infusion at 5mg per hour and titrated till chest secretions were cleared and atropinization was obtained. Inj pralidoxime 2g i.v stat given and continued for 3days. Stomach wash given and activated charcoal mixed with water and given via ryles tube. Patient was started on empirical broad spectrum i.v antibiotics.

Table 1. Investigations on the day of admission

INVESTIGATION	VALUE
Haemoglobin	14.2g%
WBC count	23,200/cu mm
Differential count	N- 52% ; L-44% ;M-4%
Platelet count	410000/cu mm
RBS	89 mg/dl
Urea	26 mg/dl
Creatinine	0.9 mg/dl
Arterial blood gas analysis	Metabolic acidosis
ECG	Sinus tachycardia
Chest Xray	B/L heterogenous opacities

Serum Cholinestrase level was greatly reduced - **281** (normal 3930 to 10800)

CK TOTAL – 934 (Elevated)

ET Tube culture – was positive for **citrobacter species** sensitive for **ceftazidime & clavulanic acid, levofloxacin and imipenem.**

Urinary myoglobin level – 800ug/dl (upto 1000ug/dl)

URINE ROUTINE

Albumin: +

Sugar: nil

Pus cells: 2-3 cells

Yeast cells were present

RBCs: nil

URINE MICROSCOPY: shows plenty of dirty haemogranular and muddy casts

Table 2. Renal parameters during hospital stay

Day from admission	Serum urea in mg/dl	Serum creatinine in mg/dl
On admission	26	0.9
3rd day	46	1.3
4th day	79	2.4
5th day	89	2.5
6th day	93	2.6
7th day	105	3.3
9th day	114	3.0
10th day	112	2.9
11th day	105	2.5
13th day	111	2.6
15th day	91	2.1
16th day	80	1.8
17th day	95	1.5
19th day	84	1.1
21st day	66	0.9
23rd day	79	1.0
25th day	62	0.8

The renal parameters as shown in the table gradually increased. The patient was diagnosed to have **Acute tubular necrosis** (ATN) probably toxin induced or due to rhabdomyolysis but urinary myoglobin levels were normal. Nephrologist opinion was obtained and was advised to maintain an intake of around 3litres per day to maintain a normal urine output. She had diuresis and her renal parameters gradually improved.

The patient on day4 of admission she suddenly went into cardiac arrest. CPR was started and inj. Adrenaline and inj. Atropine 1cc iv stat, inotropes given and the patient was resuscitated. The patient also developed seizures (GTCS) 3 episodes involving all four limbs and was treated with benzodiazepenes (inj. Midazolam 3mg iv stat during the seizure episode). After the seizure episodes patient had continuous myoclonic jerks and phenytoin loading dose 20mg/kg iv given and put on continuous infusion of inj.Midazolam 1mg/hr for 12hours.. The patient was on prolonged ventilatory support, tracheostomy was done on day 9 of admission. Regular suctioning of the tracheostomy tube done and patient treated with iv fluids, ryles tube feeding (high protein diet), inj.phenytoin 100mg iv tds, iv antibiotics(inj. Meropenem 500mg OD), multivitamins and inj. Astymin 200ml iv bd. As the patient was bedridden for a prolonged time DVT prophylaxis was started inj. Heparin 5000units s.c bd and stockings were applied to her lower limbs. The patient was given chest and limb physiotherapy.

She gradually improved. She was conscious and oriented, obeyed commands, moved all her limbs, power was 3/5 and neck muscle weakness was still present. The patient was gradually weened off the ventilator, and shifted toward after 20days of intensive care treatment. After few days again her

sensorium deteriorated, she became drowsy, her brain stem reflexes were present (doll's eye phenomenon and pupils were equal and reacting to light), but she remained aphasic, not responding to commands, glabellar tap positive, had regurgitation of food, muscle power declined (power-0/5), reflexes absent and cognitive functions were impaired, but she was maintaining a normal BP-110/70 mm Hg and saturation 98% in room air. Her sudden neurological deterioration after apparent improvement. remained unexplained. She was then subjected to MRI Brain and Nerve conduction study. The MRI Brain revealed diffuse cerebral leukodystrophy due to demyelination probably hypoxia induced.

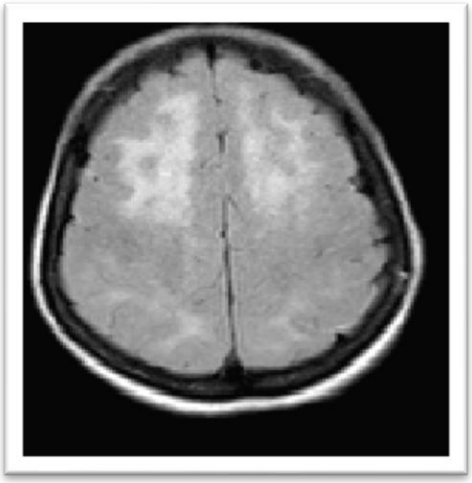

Figure 1. MRI Brain T2 FLAIR (fluid attenuated inversion recovery) axial sequence showing marked confluent hyperintensity in the both frontal regions.

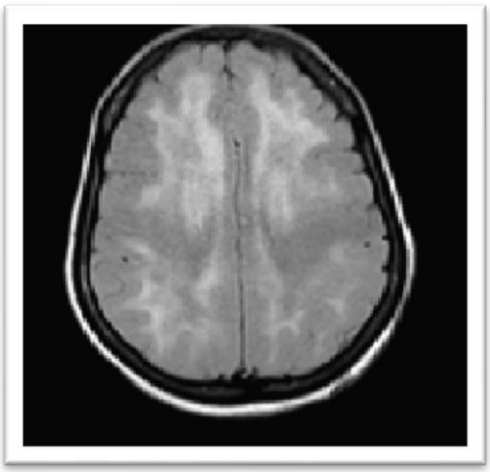

Figure 1. MRI Brain T2 FLAIR (fluid attenuated inversion recovery) axial sequence showing marked confluent hyperintensity in the bilateral frontoparietal white matter regions

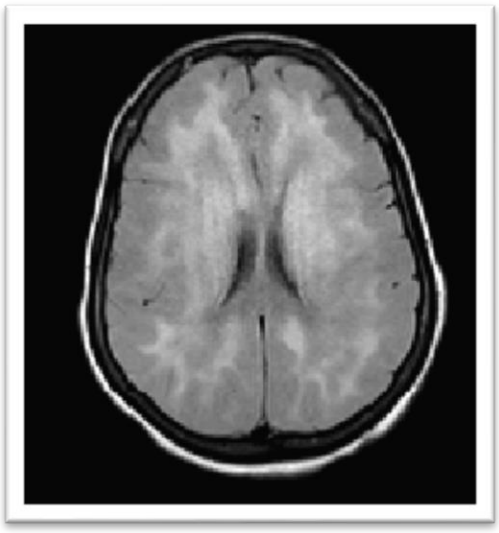

Figure 3. MRI Brain T2 FLAIR(fluid attenuated inversion recovery) axial sequence showing marked confluent hyperintensity in both centrum semiovale, corona radiata &frontoparietal white matter region

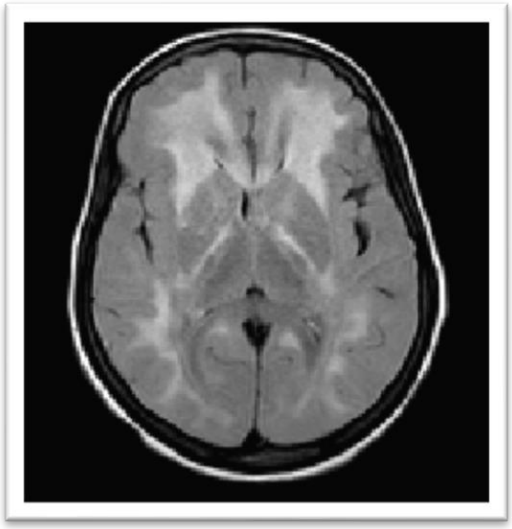

Figure 4. MRI Brain T2 FLAIR(fluid attenuated inversion recovery) axial sequence showing marked confluent hyperintensity in both periventricular, peritrigonal, internal and external capsule.

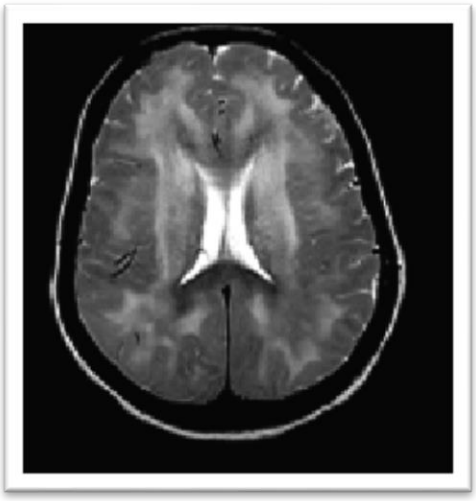

Figure 5. MRI Brain T2W axial sequence showing marked confluent hyperintensity in both frontoparietal white matter region and corona radiata.

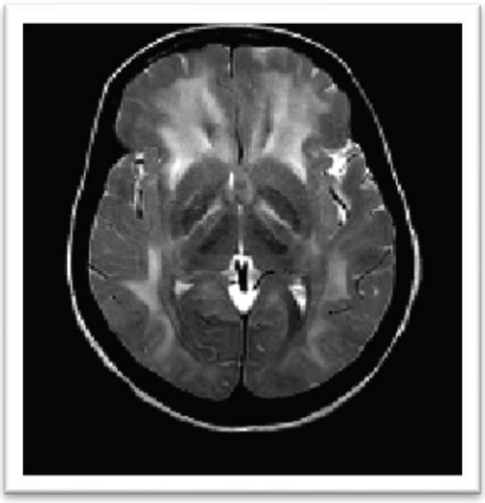

Figure 6. MRI Brain T2W axial sequence showing marked confluent hyperintensity in both periventricular, peritrigonal, internal and external capsule and frontoparietal white matter region.

The MRI BRAIN of the patient showed loss of normal grey white differentiation of the cerebral hemispheres. Marked hyperintensities seen in both periventricular regions, corpus callosum, both internal and external capsules, peritrigonal white matter regions. The bilateral symmetrical hyperintensities is marked in frontal lobe white matter. The basal ganglia, thalami and internal capsule shows abnormal signal. The lateral, third and fourth ventricles were diminished in size. The cerebellum was normal. The sulci and cisterns are effaced.

NERVE CONDUCTION STUDY showed sensory motor conduction delay of the peripheral nerves.

DISCUSSION

Organophoshorus compound poisoning (OPC):

Most of cases of organophosphorus poisoning are due to oral intake (suicidal) but farmers also develop symptoms through skin contact. These compounds are classified as 1)Alkyl compounds viz hexaethyl tetraphosphates (HETP), tetraethylpyrophosphates (TEPP), malation, cystox, dipterex, etc and 2)Aryl compounds viz parathion, paraoxon, methyl parathion, chlorothion, diazinon, etc.

The **mechanism of action** of these compounds is by inhibition of the enzyme acetylcholinesterase by phosphorylation. As a result acetylcholine(Ach) gets accumulated in the neuro muscular junction leading to 1) A muscarinic effect which increases postganglionic parasympathetic activity, 2)nicotinic stimulation, followed by paralysis and 3)CNS stimulation followed by depression.[1,2]

The **signs and symptoms** of opc poisoning are increased salivation, lachrymation, urination, defaecation, gastrointestinal distress, emesis (SLUDGE symptoms), and increased bronchial secretions with bronchoconstriction, dyspnoea and pulmonary edema. In the heart it causes bradycardia and hypotension, and in the pupils it causes constriction. The nicotinic manifestations include muscle fasciculations, cramps, weakness, areflexia and muscle paralysis. Patient may have tachycardia and hypertension due to stimulation of sympathetic ganglion. The CNS manifestations include restlessness, tremors, confusion, ataxia, weakness, convulsions, respiratory depression. The cause of death in opc poisoning is due to respiratory paralysis or intense bronchoconstriction.[3]

Some develop **intermediate syndrome** one to four days after poisoning with symptoms of motor cranial nerve palsies, neck and proximal limb weakness. Also **delayed peripheral neuropathy** can occur 1 to 5 weeks after exposure. It is

characterised by paraesthesias and cramps of the calf followed by ataxia, weakness, reflexes diminished and toe drop. The sequelae may progress for 2 to 3 months and muscle wasting is present.

The diagnosis is by a detailed history, signs and symptoms. The patient can be given 2cc of atropine which leads to atropinisation in normal but symptoms are relieved without atropinisation in poisoned. The levels of red cell and plasma cholinesterase less than 50% is suggestive of poisoned state.

Treatment is first decontamination, removal of the clothes and washing of the exposed areas with soap and water. Stomch wash should be given using a boa's tube and activated charcoal 1g/kg given via ryles tube. Oximes, Pralidoxime which is a specific cholinesterase reactivator can be given at a dose of 2g slow iv or infusion and can be repeated every 6 to 12 hours upto 48 hours. The antidote for opc poisoning is inj. Atropine which is given as 2 to 4 mg iv and the dose is repeated til the bronchial secretions are cleared. Inj. Atropine can also be given as continuous infusion and titrated. If the patient develops seizures benzodiazepenes can be given and if seizures persists inj. Phenytoin 20mg/kg iv is given. In case of respiratory failure ventilatory support and antibiotics may be necessary.[2,3]

Acute renal failure in organophosphorus poisoning

Acute renal failure (ARF) in opc poisoning is a very rare complication. The exact pathophysiology of ARF in opc poisoning is not clearly understood. Our patient had elevated renal parameters on day3 of admission which gradually increased. The patient had diuresis, her urine output was around 2500ml per day probably due to a direct injury to the renal tubules. Renal injury is more frequent in severe poisoning, although the effects may not be related to the degree of acetylcholinesterase inhibition. There have been reports of oliguric and non-oliguric acute renal failure, proteinuria and acute tubular necrosis in opc poisoning. The cause may be due to direct damage to the distal convoluted tubule, rhabdomyolysis, an increase in oxidative stress and hypovolaemia due to dehydration. Renal failure may be fatal, since substitutive renal treatments have proven unsatisfactory. This could be due to the a high distribution volume, with a low blood level, tissue accumulation and slow release; however, there are few reports of successful treatment with haemofiltration in patients with ARF due to opc poisoning.[4,5]

Delayed post-hypoxic leukoencephalopathy (DPHL)

This again is a rare condition, that may occur after prolonged cerebral hypo-oxygenation. The syndrome has a classic biphasic presentation, were there is full recovery from comatose state which is followed after few days to weeks usually varying between 1 to 3 weeks later by an acute onset of neuropsychiatric findings including disorientation, amnesia, frontal release signs, parkinsonism, hyper- reflexia, akinetic-mutism or psychosis. Magnetic resonance imaging (MRI) of the brain in such cases demonstrates diffuse demyelination of the cerebral white matter, sparing the posterior fossa. It is also named **delayed post-anoxic leukoencephalopathy," "delayed post-anoxic encephalopathy", "delayed post-hypoxic encephalopathy", "and "delayed neurologic sequelae".**[6]

A common presenting history of cases of DPHL is a preceding condition leading to a period of prolonged cerebral hypoxia. The previously described cases of DPHL were caused by carbon monoxide (CO) poisoning. The other causes were in association with surgical anaesthesia complications, cardiac arrest, asphyxial gas poisoning, strangulation, hemorrhagic shock, and overdoses of opiates or benzodiazepines. This results in 1)hypoxic hypoxia, 2) anemic hypoxia (as in CO poisoning), or 3) ischemic hypoxia (decreased cerebral blood flow). Following such a period of cerebral hypoxia there is a lucid interval usually lasting between 7 to 21 days, but can vary from 2 to 40 days. After this period the patient deteriorates and develops the neurological manifestations: parkinsonism or akinetic-mutism . In addition parkinsonian motor features- (tremors, rigidity, masked facies, short stepped gait), dystonic posturing, apathy, hallucinations, agitation, may also be present.

These patients have varying degree of cognitive impairment and slow verbal responses. Akinetic-mute patients are profoundly apathetic, develop functional bowel and bladder incontinence, minimal responses to pain, and crying or pathologic laughter. Sometimes DPHL cases are misdiagnosed as catatonia. The more severe symptoms are quadriparesis and near-blindness,

which occur with more severe cerebral hypo-oxygenation such as hemorrhagic shock or prolonged respiratory arrest during anaesthetic complications. Examination may show frontal release signs (snout, glabellar tap) and pyramidal signs such as hyper-reflexia and Babinski response positive. As the cognitive symptoms are involved early a detailed testing is difficult to obtain. The pathology may involve the cerebral white matter as this region is supplied by widely spaced arterioles with few anastomoses and as a result not able to compensate for hypoxia or hypoperfusion as the grey matter or posterior fossa. Another possible explanation for DPHL is that hypoperfusion or hypo-oxygenation restricted to cerebral white matter which may result in delayed apoptosis of the oligodendrocytes responsible for myelin production These oligodendrocytes are more susceptible to glutamate-induced excitotoxicity. Also ATP depletion may lead to release of glutamate from oligodentrocytes, which in turn triggers calcium influx and further apoptotis. Finally, inflammatory responses to damaged myelin is the other effects of hypoxemia.[7]

Diagnosis of Delayed post-hypoxic leukoencephalopathy

There is no widely accepted criteria for diagnosis of DPHL, diagnosis can be made with a clear history and testing of the patient is done. The differential diagnosis can be quite broad, if circumstance surrounding the initial hypoxic event is unclear. EEG shows generalized delta range slowing which is indicative of diffuse encephalopathy and this can be seen in more than half of cases. Other causes should be ruled out before coming to a diagnosis of DPHL. Serum study should be done to rule out medical causes of both dementia and delirium, such as uremic encephalopathy, parkinsonism due to liver failure, vitB12 deficiency, hypothyroidism, sepsis of any focus and toxicology. A lumbar puncture may be needed to rule out encephalitis after CT Brain and optic fundoscopy to rule out raised intracranial pressure which may itself clinch the diagnosis. The presence of myelin basic protein in the CSF analysis is a marker of acute widespread demyelination and can be a valuable test in suspected DHPL.

Computed tomography (CT) shows diffuse hypodensity of white matter is strongly suggestive of acute demyelination. MRI Brain shows diffuse hyperintensity of cerebral white matter in T2-based sequences, in the region of the dorsal frontal and parietal lobes (centrum semiovale). DPHL characteristically spares the ventral frontal and temporal lobar white matter, cerebellar dentate nuclei and anterior limb of the internal capsule. Globus pallidus, is usually affected, but thalamus or midbrain may be involved. T2 hyperintensity appears within 48 hours after the initial hypoxia. The clinical history and distribution of white matter changes are generally sufficient to make a diagnosis of DPHL, as the axons and oligodendroglia are largely spared in DPHL and once alternative differential diagnosis have been excluded. The other modalities used are MR-spectroscopy (MRS) and diffusion tensor imaging (DTI) and they are for research purposes.[8,9]

The likelihood of recovery is inversely related to the age of the patient. Most patients improved within 3 to 6 months. A majority of those who survive the initial period demonstrate significant recovery but most of them have at least some lasting cognitive deficits or neurologic signs such as attention, working memory and control of emotions are most common involved.

Treatment of DPHL is **supportive care** during the initial first two weeks after the occurance of the neuropsychiatric symptoms of DPHL. Immunotherapy (with steroids and plasmapheresis) has been unsuccessful. The supportive treatment includes physical therapy, occupational therapy, speech therapy, recreation therapy, and respiratory therapy when necessary. **Acetylcholinesterase inhibitors** (donepezil, rivastigmine, galantamine, dimebolin) may be tried for cognitive sequelae of DPHL. **Amantadine** tried in these patients has shown promise for treatment of these frontal-subcortical deficits and can be used along with other n-methyl-daspartate antagonists such as **memantine** could a be considered in a case of DPHL[7-9]

The rarity and the complexity of this case were the prime reasons to publishing this caser report, however we also intend to create awareness and to enable better treatment prospects to be made available for DPHL in future.

CONCLUSION

The rarity and the complexity of this case were the prime reasons to publishing this caser report, however we also intend to create awareness and to enable better treatment prospects to be made available for DPHL in future.

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