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Neuroleptic malignant-like syndrome: a complication of acute organophosphate poisoning

We report a 60-yr-old woman with schizophrenia, who manifested a neuroleptic malignant (NM)-like syndrome after acute organophosphate poisoning (OPP). She attempted suicide by ingesting 40% emulsions of DMTP (S-2,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-yl-methyl O,O-dimethyl phosphorodithioate) 100 ml. On admission, she was unconscious and demonstrated convulsions, depressed respiratory movements, miosis and profuse salivation. Plasma cholinesterase concentration ($842 \text{ IU} \cdot \text{L}^{-1}$) was very low and OPP was diagnosed. She was treated with gastric lavage, atropine and pralidoxime (PAM). By the seventh day after admission, symptoms of OPP disappeared and serum ChE had recovered to a sub-normal level. On the 13th day, she demonstrated coma, high fever (41.0°C) and lead-pipe rigidity. Serum CPK was increased ($1631 \text{ IU} \cdot \text{L}^{-1}$). Dantrolene sodium iv was administered for three days. Body temperature began to decrease in 24 hr, and her consciousness, muscle rigidity and other neurological symptoms returned to normal by the 16th day after admission. She was discharged from the hospital without sequelae 55 days after admission. We conclude that OPP can predispose to an NM-like syndrome and that dantrolene may be effective in the management.

Cette observation décrit une réaction identique au syndrome malin des neuroleptiques (SMN) survenue chez une femme de

60 ans à la suite d'un empoisonnement organophosphoré (EOP) aigu. Il s'agit d'une tentative de suicide par ingestion de 100 ml d'émulsion à 40% de DMTP (S-2,3-dihydro-5-méthoxy-2-oxo-1,3,4-thiadiazol-3-yl-méthyl O,O-diméthyl phosphorodithioate). À l'admission, elle est inconsciente et en crise convulsive, sa respiration est déprimée, elle est en myosis et elle salive avec profusion. La cholinestérase plasmatique est très basse ($842 \text{ UI} \cdot \text{L}^{-1}$) et un EOP est diagnostiqué. Elle reçoit des lavages gastriques, de l'atropine et de la pralidoxime (PAM). Au septième jour de l'admission, les symptômes de l'EOP régressent et la ChE plasmatique a récupéré à un niveau presque normal. Le 13e jour, elle devient comateuse, hyperthermique (41°C) et manifeste une rigidité en tuyau de plomb. Le CPK plasmatique augmente ($1631 \text{ UI} \cdot \text{L}^{-1}$). On lui administre du dantrolène sodique iv pendant trois jours. La température commence à diminuer en 24 h et la conscience, la rigidité musculaire et les autres symptômes neurologiques reviennent à la normale le 16e jour après l'admission. Elle reçoit son congé de l'hôpital sans séquelles 55 jours après son admission. Les auteurs concluent que l'EOP peut prédisposer à des manifestations identiques au syndrome malin des neuroleptiques et que le dantrolène peut être efficace pour le traitement.

Key words

COMPLICATIONS: neuroleptic malignant syndrome;
ENZYMES: cholinesterase, organophosphate poisoning;
POISONING: organophosphate insecticide.

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Organophosphate is one of the most frequent causes of death by pesticide poisoning in Japan. Some patients who survive the acute phase of organophosphate poisoning (OPP) may suffer relapse of toxic symptoms (intermediate type)^{1,2} or delayed polyneuropathy.³ Neuroleptic malignant syndrome (NMS) has also been described as a complication of OPP.^{4,5} We report a schizophrenic patient who developed a neuroleptic malignant (NM)-like syndrome after toxic symptoms of OPP had abated.

Case report

A 60-yr-old woman was found stuporous after ingesting 40% DMTP* emulsion 100 ml. She was a known schizo-

*S-2,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-yl-methyl O,O-dimethyl phosphorodithioate.

phrenic and had undergone frontal lobotomy at the age of 20 yr. Since then she had been free from medications.

On admission, she did not respond to painful stimuli, and showed tonic and clonic convulsions (Figure). Although the blood pressure was maintained at 120/80 mmHg, she showed frequent extra-systoles and respiration was irregular. Both pupils were constricted to pin-hole size and profuse salivation was observed. She was afebrile and extrapyramidal signs were not observed. Laboratory findings revealed that plasma ChE (842 IU·L⁻¹) was less than one fifth of normal.² The concentrations of CPK, CK-MB, LDH and blood glucose were increased to 870 IU·L⁻¹, 122 IU·L⁻¹, 960 mg·dl⁻¹, and 254 mg·dl⁻¹, respectively. Arterial blood gas analysis showed pH 7.29, PCO₂ 43 mmHg, PO₂ 80 mmHg and base excess -5.5 mEq·L⁻¹. Chest x-ray showed mild pulmonary congestion. Although 5 Hz theta waves were dominant in the EEG, no signs of laterality were observed. A naso-gastric tube was inserted and gastric lavage was performed with two litres of warmed normal saline. Oxygen, 3 L·min⁻¹, was administered by face mask. Intravenous boluses of atropine 0.5 mg were repeated every three hours for three days and infusions of pralidoxime (PAM) 1000 mg were given every 12 hr for two days. A bolus of phenytoin 250 mg *iv* was administered for convulsions.

On the second day after admission, plasma ChE concentration was still low (1108 IU·L⁻¹) and she remained unconscious, but was responding to painful stimuli. Most of her symptoms including convulsions, miosis, excess salivation and extra-systoles disappeared. On the third day, as her blood pressure decreased to 68/48 mmHg, fluid loading with 2.5 L lactated Ringer and dopamine hydrochloride 10 µg·⁻¹·kg⁻¹·min⁻¹ were given. Although temperature was increased to 38.0°C temporarily, it decreased to normal with surface cooling and diclofenac sodium 50 mg *pr*. On the fourth day, her blood pressure was normal (120/80 mmHg) without dopamine infusion and she responded to verbal commands. On the seventh day, she was alert and well-oriented. Plasma ChE concentration was 3367 IU·L⁻¹, while CPK and CK-MB had decreased to 165 IU·L⁻¹ and 26 IU·L⁻¹, respectively.

On the 13th day after admission, she became comatose, and body temperature increased to 41.0°C. Extrapyramidal symptoms such as lead-pipe rigidity, buccofacial dyskinesia and sialorrhoea were observed. Blood pressure was increased to 160/60 mmHg and she underwent considerable fluctuation in blood pressure during the day. The pulse rate was 120 min⁻¹ with normal sinus rhythm, respiration was irregular and tachypnoeic (30 breaths·min⁻¹), and she perspired profusely. Laboratory findings showed that serum CPK and LDH had in-

FIGURE Clinical course.

creased to 1631 IU·L⁻¹ and 1031 IU·L⁻¹, respectively, while plasma ChE concentration was 3694 IU·L⁻¹. Although white blood cell count increased to 14500 mm⁻³, no foci of infection were recognized on physical examination and blood cultures taken on the 13th day did not reveal bacterial infections. High concentrations of myoglobin (125 ng·ml⁻¹) were detected in the urine.

Dantrolene sodium was administered at a rate of 80 mg (2.1 mg·kg⁻¹) a day for three days. The temperature began to decrease 24 hr after initiation of dantrolene, and she became afebrile on the 16th day. Her consciousness, muscle rigidity and other neurological symptoms gradually improved and returned to normal by the 16th day. Dantrolene 100 mg·day⁻¹ for three days *po* was given after discontinuation of intravenous administration. On the 21st day, plasma CPK and ChE concentrations had recovered to normal (129 mg·dl⁻¹ and 4627 IU·L⁻¹). She was discharged from the hospital without sequelae 55 days after admission.

Discussion

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal response that occurs in some patients exposed to neuroleptic medication. The core features include diffuse muscular rigidity, hyperthermia, autonomic instability and altered consciousness. Associated findings include leucocytosis and hyperkalaemia and increased serum CPK.^{6,7} Some cases have been reported in the absence of a history of neuroleptic treatments, for example due to dopamine-depleting drugs such as tetra- benzazine in Huntington's chorea,⁸ and withdrawal of dopamine agonists such as levodopa in Parkinson's disease.⁹

On the other hand, acute organophosphate poisoning (OPP) is one of the most common types of pesticide poisoning in Japan. This patient was supposed to have ingested 40 g of DMTP, which is more than 20 times the LD₅₀ in mice (52 mg·kg⁻¹). The OPP is caused

by excessive acetylcholine activity at postsynaptic membrane in the central nervous systems (CNS), nicotinic receptors of preganglionic sympathetic and parasympathetic ganglia, neuromuscular junction and muscarinic receptors of post-ganglionic parasympathetic fibres. Typical symptoms related to CNS disorder by OPP are restlessness, depressed consciousness and tonic-clonic convulsions.¹⁰ Extrapyramidal symptoms including chorea and dystonic reactions are also reported.¹¹

Relapses of toxic symptoms may occur after patients have recovered from acute OPP. Patients with intermediate OPP syndrome manifest muscular weakness involving the respiratory muscles, proximal limb muscles, neck flexors and muscles innervated by some cranial nerves. These symptoms appear suddenly, 24 to 96 hr after the onset of OPP and last for 5 to 18 days.^{1,2} The chronic effects of OPP can be classified into neurological and non-neurological features.¹ The former includes polyneuropathies,^{3,4} and the latter liver dysfunction, dermatitis, coagulopathies, and fetal abnormalities. Differing from varieties of complications manifested in the recovery period of OPP, NMS is very rare and only a few cases^{4,5} have been reported in relation to OPP.

The symptoms in our patient were consistent with the major and minor categories of Levenson's criteria for NMS (Table)⁷ except that she had never been exposed to any neuroleptic or other dopamine receptor-blocking drugs. The symptoms in this case were also consistent with those of Stauder's lethal catatonia in schizophrenic patients.^{12,13} Lethal catatonia is characterized by excitement, stupor, high fever, overtoneity of the muscles and a high mortality rate. Many investigators consider that this is clinically similar to and indistinguishable from NMS. However, symptoms such as fever as high as 41°C, rhabdomyolysis with increased serum CPK and myoglobinuria in our patient showed more conformity with the clinical features of NMS than with those of lethal catatonia.¹⁴

Regarding the relationship between NM-like syndrome and OPP, the following speculation can be made. First, the patient manifested psychiatric symptoms of schizophrenia which resulted in excitement, insomnia, exhaustion, dehydration and malnutrition. Exhaustion and other physical disorders accelerated by OPP could predispose to NML.⁶ Second, it is suggested that OPP causes imbalance of dopamine synthesis by increasing the concentration of acetylcholine in the brain.¹¹ These changes in the brain may be the mechanism that induces the extrapyramidal symptoms as well as the NM-like syndrome in OPP. The patient was initially treated for OPP with atropine and pralidoxime (PAM). This treatment was quite effective and she seemed to have recovered from OPP, when the NM-like syndrome suddenly appeared.

TABLE Levenson's criteria in the diagnosis of neuroleptic malignant syndrome.

Major manifestations	Minor manifestations
Fever	Tachycardia
Rigidity	Abnormal blood pressure
Increased CPK	Tachypnoea
	Altered consciousness
	Diaphoresis
	Leucocytosis

The presence of all three major, or two major and four minor manifestations indicate a high probability of the presence of neuroleptic malignant syndrome.

Treatment for NMS includes discontinuation of neuroleptics, reduction of body temperature, respiratory support and drug therapy using a combination of bromocriptine and dantrolene.^{6,14} Bromocriptine produces its effect through central dopaminergic mechanisms. Dantrolene reduces muscle tone by a peripheral effect, while a central effect is also suggested. In our patient, body temperature, muscle tone, instability of blood pressure and consciousness returned to normal after dantrolene therapy. Dantrolene is also known to be effective in lethal catatonia.¹⁴

In conclusion, OPP may predispose a NM-like syndrome and administration of dantrolene may be effective in its treatment.

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