Short report

Late onset Isofenphos neurotoxicity

AMIRAM CATZ,*† BARUCH CHEN,† ITZHAK JUTRIN,† LAZAR MENDELSON*

From the Loewenstein Rehabilitation Center,* Raanana, and Department of Internal Medicine, Meir Hospital, Kfar-Sava,† Tel-Aviv University Sackler School of Medicine, and the IDF Medical Corps† Israel

SUMMARY Late progressive polyneuropathy followed by pyramidal findings in a 20 year old agricultural labourer who ingested Isofenphos solution during his work, is presented. The patient was confined to a wheelchair within 6 weeks, regained walking ability within 6 months, and a 23 months' follow up revealed slight additional clinical improvement with minimal progression of the pyramidal signs. The neuropathic clinical manifestations, the EMG and the nerve conduction studies were compatible with a pathology of a distal, mainly axonal, mainly motor neuropathy.

Organo-phosphorus compounds have a well known immediate muscarinic neurotoxic effect precipitated by the acute inhibition of acetylcholinesterase. Late onset non-muscarinic neurological effects of these compounds have been reported as well.¹⁻⁴

A case of ascending, mainly motor, neuropathy which appeared 2 weeks after ingestion of Isofenphos and which was followed up for 23 months is presented. To the best of our knowledge, this is the first description of a case of late onset Isofenphos neurotoxicity in man.

Case report

A 20 year old healthy agriculture worker accidentally ingested a few millilitres of diluted insecticide solution which was thrown off into his face while he was using it for spraying flowers. The solution contained 0.75 mg/ml Isofenphos (0-ethyl-0 (2-isopropoxy-carbonyl) phenyl isopropyl phosphoramidothioate) and 2 mg/ml Maneb (manganese ethylene-1,2-bis-dithiocarbamate). He was first attended to by a local physician who gave him an atropine injection, then taken to the emergency unit of a general hospital, where no clinical signs of organophosphorus poisoning were found, and serum cholinesterase level was 2.4 units/ml (normal laboratory values: 3-6). Several hours later he experienced weakness, dyspnoea and vomiting from which he recovered about 16 hours after the exposure. Two weeks later, while at home, he contracted pain in the calves, followed by gait

impairment and weakness in the hands. Readmitted to hospital 3 weeks after the initial event, his general physical examination was normal and no recent history of a febrile disease was disclosed. However, neurological examination revealed hypotonia of the hand flexors, Achilles hyporeflexia and a mild sensory deficit in a "gloves and stockings" distribution. Blood, urine and CSF laboratory tests for screening possible neuropathic aetiologies produced normal findings. Pulmonary function tests and radiographs were normal. Serum cholinesterase level was 6.3 units/ml.

A process of subacute motor deterioration took place. Until the 5th week after the intoxication, paralysis ascended proximally to the point where the patient became confined to a wheelchair. Two weeks later he could hardly use his hands. Anal tonus and bulbocavernosus reflexes were reduced, but the patient remained continent. During the following months the patient gradually recovered. The neuropathic deficit diminished, first in proximal and later in more distal parts of the limbs (fig). The figure gives a detailed temporal profile of various muscle groups strength, scored from 0 to 5 according to MRC grading.⁵ With the motor improvement, the sensory impairment, which had been minimal to begin with, almost disappeared; however, signs of an upper motor neuron impairment developed. Hyperreflexia became evident (except at the ankles) and pathological Hoffman's Trousseau's and Babinski's reflexes were noticed.

Six months after exposure to Isofenphos the patient could walk with the aid of two wooden canes and elastic bandaging of the dropped feet. He was able to stand up from a sitting position with the aid of one cane, and attained an almost complete independence in daily living functions. Twenty-three months after the intoxication the functional state was minimally improved and the pyramidal signs were slightly more prominent.

Electromyographic (EMG) findings which were compatible with denervation and re-innervation developed in

Address for reprint requests: Dr Amiram Catz, Loewenstein Hospital, Raanawa, PO Box 3, Israel.

Received 31 March 1988 and in revised form 16 May 1988.
Accepted 27 May 1988

Fig. Curves: average muscular strength up to 103 weeks after the intoxication. Arrows: EMG pattern in clinically deteriorated or improving muscles 8, 25 and 103 weeks after the exposure.

parallel to the clinical course: "Denervation pattern" was elicited in deteriorating or paralysed muscles, while EMG characteristics of re-innervation were found in those muscles which showed improving strength (fig). Denervation was expressed by fibrillation potentials, positive sharp waves and reduced motor units recruitment, and re-innervation by partial or complete regaining of the normal interference pattern, the disappearance of the abnormal spontaneous electrical activity and the appearance of compound, polyphasic waves.⁶ Motor nerve conduction studies presented similar temporal changes. In these studies, impairment was prominent in long nerves rather than in shorter ones and in distal rather than in proximal parts of the damaged nerves. Amplitudes of evoked muscle potentials were reduced, as in cases of axonopathies, to a greater extent than were nerve conduction measurements (table).

Discussion

The described neuropathy appeared 2 weeks after ingestion of insecticide solution without a prior febrile episode or any data which could point to any other known cause. In addition to Isofenphos, the solution

included Maneb, a manganese carbamate fungicide of low toxicity. The manganese moiety is of little toxicological significance.⁷ The carbamate component is potentially toxic, however, no references which clearly relate subacute neurotoxicity to carbamate esters have been found.⁸ The estimated exposure dose of the Maneb was very low, about 0.25 mg/kg while rat oral LD50 is about 4500 mg/kg. In comparison with it, the exposure dose of Isofenphos was about 0.1 mg/kg while its male rat oral LD50 is 38.7 mg/kg.

Serum cholinesterase was slightly below the normal range during the acute phase. Erythrocyte cholinesterase would probably have been a better diagnostic test for organophosphorus exposure, but this measurement was not available. However, indication of exposure can be obtained by serum cholinesterase level and quite commonly it is more sensitive to inhibitors than true cholinesterase.⁹ It should also be noted that although close to the normal range, serum cholinesterase level in the acute phase was about 38% of its level 3 weeks later which probably reflected the patient's pre-exposure level.

Table Changes in nerve conduction and evoked muscle potentials 4 to 103 weeks after the intoxication

		Distal motor latency (ms)	Motor conduction velocity (m/s)	Amplitude of evoked muscle potentials (mV)	Nerve action potential latency (ms)
Lower limb	4 weeks	∞	*	0	*
Long nerves	25 weeks	∞	*	0	*
(Lateral popliteal and tibialis to foot muscles)	23 months	∞	*	0	*
Upper limb long nerves	4 weeks	2.9-3.4	41.4-48.1	very low	*
Median and ulnar nerve.	8 weeks	∞	*	0	3.5-4.4
Wrist to palm (DML, AMP) and cubita to wrist (CV, NAP)	25 weeks	11.2-∞	34.9	0-0.8	4.2-5.1
Upper limb shorter nerves (median to PQ and ulnar to FCU)	23 months	2.3-3.7	30.3-48.8	2.3-5.7	3.6-4.2
	25 weeks	2.6-3.0	*	0.09-2.3	*
	23 months	2.3-3.4	*	3.5-5.5	*

*Not measured. DML = distal motor latency AMP = amplitude CV = conduction velocity. NAP = nerve action potential PQ = pronator quadratus FCU = flexor carpi ulnaris.

The pathological process of organophosphorus late neuropathy is related to inhibition of the neuronal enzyme called neurotoxic esterase (NTE),¹⁰ and is described as an axonopathy, which is distal but not terminal and is precipitating a Wallerian degeneration of the more distal axon.^{11 12}

The case presented largely resembles those of late onset organophosphorus neuropathy reported previously, and its clinical, EMG and NCS findings (fig; table) were compatible with the neuronal pathology described above. Thus, it is most likely that the neuropathy was caused by the thiophosphate compound Isofenphos. Occasional cases of late neuropathy in man have been reported after single or multiple exposures to other compounds of the thiophosphate group,¹⁹ and Isofenphos delayed neuropathy has been experimentally induced in chicken,¹³ but this is the first report of a human late neurological complication induced by this compound.

References

- 1 Ecobicon DJ. Organophosphorus ester insecticides. In: *Pesticides and Neurological Diseases*. Florida: CRC Press, 1982:172-6.
- 2 Morgan JP, Penovich P. Jamaica Ginger Paralysis, Forty-seven year follow-up. *Arch Neurol* 1978;**35**: 530-2.
- 3 Cherniack MG. Organophosphorus Esters and Polyneuropathy. *Ann Int Med* 1986;**104**:264-6.
- 4 Karni A, Baniel J, Shemer J, Skurnik Y. Delayed neurotoxicity by organophosphorus compounds. *Harefuah* 1985;**108**:446-8.
- 5 Medical Research Council. Aids to the examination of the peripheral nervous system. London: Her Majesty's Stationery Office, 1976:1-2.
- 6 Goodgold J, Eberstein A. *Electrodiagnosis of Neuromuscular Disease*. Williams and Wilkins, Baltimore, 1983:228.
- 7 International Programme on Chemical Safety. Manganese. Environmental Health Criteria 17. Geneva: WHO, 1981:85.
- 8 Ecobicon DJ. Carbamic acid ester pesticides. In: *Pesticides and Neurological Diseases*. Florida: CRC Press, 1982:223-4.
- 9 International Programme on Chemical Safety. Organophosphorus Insecticides: A general Introduction. Environmental Health Criteria 63. Geneva: WHO, 1986:97-111.
- 10 Lotti M, Becker CE, Aminoff MJ. Organophosphate polyneuropathy: Pathogenesis and prevention. *Neurology* 1984;**34**:658-62.
- 11 Taylor P. Anticholinesterase agents. In: Goodman and Gilman, eds. *The Pharmacological Basis of Therapeutics*. New York: Macmillan Publishing Co, 1980: 11-112.
- 12 Bouldin TW, Cavanagh JB. Organophosphorus neuropathy. I: A teased-fiber study of the spatiotemporal spread of axonal degeneration. *Am J Pathol* 1979;**94**:241-52.
- 13 Wilson WB, Hooper M, Chow E, Higgins RJ, Knaak JB. Antidotes and neuropathic potential of Isofenphos. *Bull Environ Contam Toxicol* 1984;**33**:386-94.