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Mini Review

Organophosphate-Induced Delayed Polyneuropathy in Man: Clinical Presentation, Mechanisms and Treatment -

Milan Jokanović[1]*, Zoran Šegrt[2], Miloš P Stojiljković[3], Dragana Ristić[2] and Bojan Kovač[2]

[1]*Experta Consulting, Belgrade, Serbia*

[2]*Military Medical Academy, Belgrade, Serbia*

[3]*Faculty of Medicine, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina*

***Address for Correspondence:** Milan Jokanović, Experta Consulting, Belgrade, Serbia, E-mail: milan.jokanovic@gmail.com

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ABSTRACT

Approximately 90 years have passed since the first cases of Organophosphate Induced Delayed Polyneuropathy (OPIDP), as the consequence of human poisoning with certain organophosphorus compounds, were described in the literature. OPIDP is a relatively rare neurodegenerative disorder in humans characterized by loss of function, ataxia and paralysis of distal parts of sensory and motor axons in peripheral nerves and ascending and descending tracts of spinal cord appearing usually 2-3 weeks after exposure. The aim of this review is to discuss clinical presentation, pathogenesis, molecular mechanisms of OPIDP in man and the possibilities of treatment.

Keywords: Organophosphorus; Organophosphate induced delayed polyneuropathy

ABBREVIATIONS

OPC: Organophosphorus Compounds; AChE: Acetylcholinesterase; OPIDP: Organophosphate-Induced Delayed Polyneuropathy; NTE: Neuropathy Target Esterase

Organophosphorus Compounds (OPC) have been used as insecticides and developed as warfare nerve agents such as soman, sarin, tabun, VX and others. Insecticide poisoning results from occupational, accidental and intentional exposure. According to the World Health Organization, about 1 million accidental and 2 million suicidal poisonings with organophosphorus insecticides are reported per year, with more than 300000 fatalities and the average mortality of more than 15% [1,2].

OPC cause several neurotoxic disorders in humans: a, the cholinergic syndrome or acute OP poisoning occurring after Acetylcholinesterase (AChE) inhibition in the nervous system; b, the intermediate syndrome; c, Chronic Organophosphate-Induced Neuropsychiatric Disorder (COPIND); and d, Organophosphate-Induced Delayed Polyneuropathy (OPIDP). While the cholinergic syndrome is caused by all OPC (depending on dose) the OPIDP is not caused by warfare nerve agents and many OP pesticides [3].

The aim of this review is to discuss clinical presentation, pathogenesis, molecular mechanisms, and possibilities of treatment of OPIDP in man where ataxia and paralysis are the most important features.

OPIDP is an interesting neurotoxic phenomenon caused by a single exposure to certain OPC with clinical effects usually appearing after 10 to 20 days or later. OPIDP is a different toxicological problem from cholinergic syndrome since it is based on different mechanisms which do not involve AChE and appear a few weeks after acute OP poisoning has been medically solved with standard therapeutic measures and patient dismissed from hospital. OPIDP is also a different syndrome from the intermediate syndrome [3].

The interest in OPIDP was increased after thousands cases of poisoning with Triorthocresyl Phosphate (TOCP) that occurred mainly due to beverage and food contamination in USA in 1930 and Morocco in 1959 [4-7]. By the end of twentieth century, there were many cases of OPIDP due to TOCP poisoning in Romania, Sri Lanka, former Yugoslavia and China. In addition to TOCP, several other OP pesticides have been reported to cause OPIDP in man (Table 1) [8-12]. Cases of OPIDP caused by pesticides were also discussed by Lotti and Moretto [9].

OPIDP is a rare neurodegenerative disorder in humans characterized by loss of function and ataxia of distal parts of sensory and motor axons in peripheral nerves and ascending and descending tracts of spinal cord. The early neurological symptoms usually are sharp, cramp-like pains in the calves, tingling in the feet and hands followed by distal numbness and paresthesia. Pain and weakness in muscles spread rapidly and patients become unsteady and unable to keep their balance. Progressive leg weakness occurs, together with depression of tendon reflexes. Symptoms may also appear in the arms and forearms. Sensory loss may be mild. Muscle tonus of the limbs gradually increase and spasticity appears in the lower limbs. Physical examination reveals distal symmetrical mainly motor polyneuropathy, with wasting and flaccid weakness of distal limb muscles, especially in the lower limbs. In severe OPIDP quadriplegia with foot and wrist drop were observed as well as mild pyramidal signs [6]. There may be some functional recovery in less severe cases with more distal involvement and sparing of spinal cord axons, but pyramidal and other signs of central neurological involvement may become more evident with time [3]. The recovery affects only sensory nerves, while motor neurons may permanently lose its function as indicated by Morgan [5] who described the lack of improvement during 47 years in 11 patients poisoned with TOCP. Tosi et al. [13] also noted the absence of any improvement after 50 years in 7 patients exposed to TOCP. However, the study reported by Wang et al. [14] conducted 13 years after TOCP poisoning of 74 patients revealed that out of 61 survivors, 35 patients almost regained normal function of limbs and work outside; 23 patients walked with

Table 1: Organophosphorus pesticides reported to cause OPIDP in man (8-12).

OP insecticide	No of cases	Location	Year
Chlorpyrifos	2	Italy, India	1986
Dichlorvos	5	Romania, Turkey, Brasil, Korea, India	1980, 2002-2006
Ethyl parathion	1	Germany	1993
Fenthion	3	USA	1985
Isofenphos	1	Israel	1987
Isofenphos/ phoxim	1	Italy	1995
Leptophos	80	USA	1974
Malathion	2	Japan, Turkey	1991, 2009
Merphos	1	USA	1977
Methamidophos	> 45	Sri Lanka, Italy, China, Turkey, USA	1981, 1998
Mevinphos	1	Serbia	2010
Mipafox	3	UK	1952
Omethoate	1	France	1972
Phosphamidon/ Mevinphos	1	China	2002
Trichlorfon	22	Romania, Iran, Japan, Hungary	1983 -1986
Trichloronat	1	Poland	1975

bilateral support and could perform housework; and 3 patients could not self-care. Neurophysiological investigations showed normal electroencephalogram and visual, brainstem auditory and somatosensory evoked potentials. Motor evoked potential obtained from the upper limbs had normal central motor conduction time, but it was delayed or absent in bilateral lower limbs. Motor and sensory nerve conduction velocity and electromyography studies were normal except for two severely affected patients.

The prognosis for functional recovery depends on the degree of pyramidal involvement with ataxia and paralysis representing a permanent outcome of severe OPIDP. It appears that clinical signs of OPIDP in children are considerably milder than in adults [4,9,14].

Electrophysiological evaluation revealed partial denervation of affected muscles with abnormal spontaneous activity (fibrillation potentials, positive sharp waves), increased insertional activity, reduced amplitude of muscle action potentials, delayed terminal motor latencies and motor conduction velocity slightly reduced or normal [4,6,15]. These findings are in accordance with the results of pathological studies showing Wallerian-type degeneration of axons mainly affecting myelin sheats with aggregation, accumulation and partial condensation of neurofilaments in the nervous system.

Several mechanisms of OPIDP have been proposed. OPIDP is initiated by phosphorylation and subsequent aging of > 70% the enzyme originally known as neurotoxic esterase, but later renamed to Neuropathy Target Esterase (NTE) in peripheral nerves [4,6]. NTE was discovered by Martin Johnson, who described its most important toxicological and biochemical features [4]. NTE is an integral membrane protein in vertebrate neurons present in all neurons, but not in glia. The active site of NTE contains Ser^{966} and two aspartates Asp^{960} and Asp^{1086} that appear essential for enzymatic activity. The physiological substrate for NTE is considered to be lysolecithin [16]. NTE regulates phospholipid metabolism and is known to be a phospholipase B [17,18]. Inactivation of NTE may reduce the degradation of phosphatidylcholine to glycerophosphocholine. The deficiency of the NTE activity may lead to abnormal accumulation of phosphatidylcholine-containing membranes in cells, which may interfere with normal membrane lipid homeostasis and fluidity affecting the initiation of neurites. Since NTE hydrolyzes lysolecithin [16,19,20], the delay in initiation of neurites may also be caused by an abnormal accumulation of lysolecithin in NTE-deficient cells [21].

NTE is involved in intracellular membrane trafficking and cell-signaling pathway between neurons and glial cells [22-24]. There is a relationship between NTE activity and the axonal maintenance since it facilitates the transport of macromolecules from the neuron to the distal ends of long axons [25].

It was also suggested that NTE may be involved in the regulation of calcium entrance into cells being responsible for the maintenance of normal function of calcium channels, and that increasing calcium activated neutral protease activity is responsible for triggering OPIDP [26].

Medical treatment of OPIDP in humans is symptomatic. Standard treatment of OPC poisoned patients comprising atropine, oxime and diazepam was not effective in treatment of OPIDP. However, there were several reports in the literature describing attempts of treatment of OPIDP in animals and these studies were reviewed by Lotti [6] and Jokanović et al. [7], but none of these treatments have been tested in patients so far.

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