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An uncommon pattern of polyneuropathy induced by lifetime exposures to drift containing organophosphate pesticides

A. Ophir [a,b,1], I. Karakis [c,1], E.D. Richter [d], J.M. Abarbanel [a], U. Wormser [b], M. Aschner [e], Y. Finkelstein [a,*]

[a] Neurology and Toxicology Service and Unit, Shaare Zedek Medical Center, Jerusalem, Israel
[b] Institute of Drug Research, School of Pharmacy, Hebrew University of Jerusalem, Israel
[c] Department of Environmental Epidemiology, Ministry of Health, Jerusalem, Israel
[d] Department of Occupational and Environmental Medicine, Faculty of Medicine, Hebrew University of Jerusalem, Israel
[e] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, USA

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ABSTRACT

The natural history of chronic peripheral polyneuropathy following lifetime low-level organophosphate (OP) exposure was investigated. A pilot study (1984–1987) conducted in rural communities in Israel detected subtle reversible in-season changes in nerve conduction patterns of 17 field workers out of 214 residents exposed to seasonal drift containing OP's. We examined 60 individuals (males: 50/60; 83.3%) from the original cohort still residing (more than 40 years) in the same communities. Exposure assessment was based on reports by Israeli institutions and the Bureau of Statistics. Information on personal status, work experience, exposures and symptoms was collected by questionnaires. The nervous system was systematically studied, evaluating cortical upper motor neurons, corticospinal tracts, lower motor neurons and peripheral nerves. Electrophysiological studies included conduction velocities, amplitudes and distal latencies of sensory and motor median, ulnar, tibial and sural nerves; F-waves for proximal nerve functions; thermal and pain thresholds for small thinly-myelinated and non-myelinated fibers; transcranial magnetic stimulation for large fibers.

Clinical and electrophysiological features of Carpal Tunnel Syndrome were found in 18% of the subjects, atypically in males only. Fingertips' tingling correlated with both axonal and myelin-dependent parameters (lower wave amplitudes and prolonged latency periods, respectively) in the sensory median nerves bilaterally. OP exposure significantly correlated to prolonged distal latency in the right median sensory nerve ($r = 0.29$; $p = 0.052$; $n = 45$) and lower wave amplitude in the right sural nerve ($p = 0.031$). These findings attest to subtle, predominantly sensory peripheral polyneuropathy following lifetime low-level exposures to drifts containing OP.

1. Introduction

Scarce clinical and epidemiological information exists on the effect of lifelong low-level exposure to organophosphates (OP) on the function of the peripheral nervous system (PNS) and spinocortical tracts. Studies of individuals with long-term, low-level exposure are suggestive of nervous system effects, but their findings are not as consistent as findings from acutely exposed individuals. This present study was carried out in adult population in a rural area and aimed to investigate this enigmatic association.

No impairment of nerve conduction, vibration sensation or motor function was detected in 45 professional pesticide applicators that had been exposed to different OP brands and had had at least one documented episode of cholinesterase (ChE) inhibition without symptoms (Ames et al., 1995). Nerve conduction velocity (NCV) studies in 24 Philipino rice field workers failed to show association between chronic OP exposure and peripheral polyneuropathy (Ofelia et al., 2003). Similarly, there was no evidence of clinical or subclinical peripheral neuropathy in 113 chemical workers who

Abbreviations: BuChE, butyrylcholinesterase; BMI, body mass index; ChE, cholinesterase; CTS, Carpal Tunnel Syndrome; CPF, Chlorpyriphos; HMO, Health Maintenance Organization; Lt., left; NCV, nerve conduction velocity; OECD, Organization for Economic Co-operation and Development; OP, organophosphate; OPIDN, OP-induced delayed neuropathy; OPIDP, OP-induced delayed polyneuropathy; PNS, peripheral nervous system; Rt., right; TMS, transcranial magnetic stimulation; TSA, thermal sensory analysis.

* Corresponding author. Tel.: +972 2 6781781; fax: +972 2 6666941.
E-mail address: yoramf@ekmd.huji.ac.il (Y. Finkelstein).

[1] These authors contributed equally to this paper which is based on AO's PhD thesis.

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had been exposed for a year to Chlorpyriphos (CPF) during its manufacturing process (Albers et al., 2004). Later dose–effect analyses of CPF exposure and peripheral nerve electrophysiology in the same study group provided support for the absence of subclinical neuropathy (Albers et al., 2007). However, workers' exposure to CPF in industrial settings differs from workers' exposure in agricultural setting or residents' exposure to CPF drift. Production workers' exposure is continuous, while agricultural workers and residents are intermittently exposed in-season to fluctuating levels of CPF. In both cases, first and foremost in industrial settings, data are not readily available on exposures and risks.

NCV values were negatively associated with lifetime days of pesticide application in 31 male Korean farmers who had been occupationally exposed to OP pesticides for 24 years, 28.5 application days per year (mean values) (Park et al., 2012). Although all mean NCV values remained within normal limits, significant in-season differences were found in the sensory median and sural nerves. The majority of the farmers in the study group raised vegetables in greenhouses; and more than a half of them had experienced acute OP poisoning. Therefore, the farmers should be referred to as highly exposed individuals with intermittent episodes of acute OP poisoning and consequent delayed OP-induced polyneuropathy (OPIDN). Sixty-eight pesticide applicators that used mainly Guthion, Diazinon and CPF were examined off-season alongside with 68 matched controls. Under these occupational settings, the applicators showed a significant decrease in the vibrotactile sensitivity in their hands (Stokes et al., 1995). Peripheral nervous system (PNS) changes were shown after repeated occupational OP exposures (McConnell et al., 1994; Steenland et al., 1994). Among 612 sheep dippers, a weak positive association was found between cumulative occupational exposure to OP pesticides and indices of peripheral neuropathy. However, the significance of this finding was dependent on the inclusion of the four highest exposed individuals, two of whom were symptomatic. Significance could not be shown among the overwhelming majority of dippers. No association was found between cumulative OP exposure and thermal or vibratory sensory thresholds. The authors concluded that long term health effects may occur in at least some sheep dippers exposed to OP over their working life. Neuropathy, when clinically diagnosed and neurophysiologically established (in a few cases) was predominantly of the sensory type (Pilkington et al., 2001).

Our previous studies (EDR) in sentinel populations of workers and community groups in Israel showed OP exposures to lead to mild in-season transient dysfunction of the PNS (Richter et al., 1980, 1992, 1997). The parameters of nerve conduction amplitudes were impaired in the sensory nerves of agricultural workers and residents in kibbutzim (communal agricultural settlements) in the Hula Valley who were continuously exposed to OP drift from aerial spraying of the neighboring fields (Richter et al., 1992). Other studies examined groups of pilots, ground-crews, and field workers. In all these groups, evidence of exposure-illness association was found, although acute poisoning was not observed. Symptoms of fingertips' tingling in the hands were observed in individuals with high alkyl phosphate urinary levels, but normal plasma ChE activity (Richter et al., 1984, 1986).

We have extended the previous study in Hula Valley in light of these findings. Our working hypothesis was that continuous seasonal exposures to OP drift for lifetime might cause cumulative and probably detectable damage to the PNS.

We reasoned that the OP-induced subclinical PNS changes that were observed in previous studies might exert a small effect on the quality of life or day-to-day functioning. Notably, no study on the PNS effects has followed up its subjects longitudinally for decades. Consequently, the comprehensive natural history of chronic OP neurotoxicity has yet to be deciphered. This issue is of importance, given that ubiquitous rural populations are exposed permanently to OP drifts. Therefore, the present study with lifetime follow-up addresses the natural history of chronic peripheral neuropathy that might follow decades of low-level OP exposure.

2. Methods

A cross-sectional study in adult population was designed to explore the association between OP exposure and the electrophysiological function of the corticospinal tracts and the PNS.

2.1. Population

An adult population residing in five Kibbutzim in the Hula Valley in Northern Israel was recruited by the local Health Maintenance Organization (HMO) clinics. The studied group included 60 individuals 50 of whom were males (83.3%), the mean age of whom was 56.2 years (range 37–69 years) residing in the Hula Valley for more than 40 years. The males were non-significantly elder ($p = 0.075$) than the females (57.4 ± 6.1 years vs. 50.4 ± 10.8 years, respectively). The duration of environmental exposure to pesticides was similar ($p = 0.348$) in males (46.3 ± 13.8 years) and females (41.9 ± 10.2 years). Their cumulative periods of manual labor occupations were sixteen individuals (9 males and 7 females) had a manual labor job up to 10 years. The rates of males and females having a manual labor job up to 10 years are different (9/49 vs. 7/10, respectively; $p = 0.002$). Thirteen individuals (11 males and 2 females) had a manual labor job for 10–20 years; and 30 individuals (29 males and 1 female) for more than 20 years cumulatively.

2.2. Exposure assessment

The study was carried out in a rural area with extensively cultivated fields in proximity to the inhabitant's houses (50–100 m in many cases), as shown in Fig. 1.

OP pesticides consisted 87% of the total amount of agricultural pesticides used in Israel in the 1980s (Gordon and Hirsch, 1986); and 70–80% of the total amount of pesticides sprayed from the air in the same period (Finkelstein et al., 2011). The ratio of quantity (tons) of active ingredient in pesticides sold per 1000 persons in Israel in 2008 was 1.0. This ratio was higher in Israel than in any other OECD (Organization for Economic Co-operation and Development) country except Japan (Central Bureau of Statistics, Israel, 2013). Ratio of the quantity (tons) of active ingredients in pesticides sold annually per 1000 dunam (dunam = 1000 square meters or 0.1 hectare) of agricultural land including field crops and vegetables in Israel was 3.5 in 2008. This was the highest ratio in the OECD member countries. Most of the OECD countries had a significantly lower ratio of less than 1.0 ton of active ingredients sold per 1000 dunam (100 hectares) (Central Bureau of Statistics, Israel, 2012). This ratio in Galilee-Golan region (including Hula Valley) was the highest in Israel – 6.79 tons per 1000 dunam in 1998, whereas the ratios in all other regions Israel ranged between 1.26 tons and 4.23 tons per 1000 dunam (100 hectares) (Bar Ilan et al., 2000; Migal – Galilee Research Institute, 2001).

The water quality was monitored in the Jordan River, which irrigates the Hula Valley and down streams toward the Sea of Galilee. The annual 2005–2010 reports specified eight brands of OP pesticides traced in the river and the Sea of Galilee. OP degradation products were not monitored routinely in the Sea of Galilee basin (Bar-Ilan and Malman, 2007; Israel Oceanographic and Limnological Research, 2012).

2.3. The definition of exposure variable and scoring of individual exposures

The extent of OP exposure was defined by a combined score of both occupational and environmental exposures. The level of