ELECTRONIC PAPER

Muscular strength and vibration thresholds during two years after acute poisoning with organophosphate insecticides

J Miranda, R McConnell, C Wesseling, R Cuadra, E Delgado, E Torres, M Keifer, I Lundberg

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See end of article for authors' affiliations

Correspondence to: Dr J Miranda, Departamento de Medicina Preventiva, Facultad de Medicina, UNAN-León, León, Nicaragua, Central América; jamilette.miranda@smd.sll.se

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Aims: To evaluate the association of acute organophosphate (OP) poisoning with chronic sensory and motor neurological impairment.

Methods: This study concerns the third of a series of three examinations of hand strength and vibration thresholds in a two year period after acute OP poisoning among 48 Nicaraguan men. The first two examinations were performed at hospital discharge and seven weeks after poisoning, and the present examination two years later. Twenty eight cattle ranchers and fishermen who had never experienced pesticide poisoning were examined as controls, also three times over the two year period. The poisonings were categorised as caused by ''non-neuropathic'' OPs and ''neuropathic'' OPs, each subdivided in moderate and severe poisonings.

Results: Men poisoned with OP insecticides had persistent reduced hand strength. We previously reported weakness at hospital discharge for OP poisoned in all categories that worsened seven weeks later for those severely poisoned with neuropathic OPs. Strength improved over time, but the poisoned were still weaker than controls two years after the poisoning, most noticeably among the subjects most severely poisoned with neuropathic OPs. Also, index finger and toe vibration thresholds were slightly increased at the end of the two year period, among men with OP poisonings in all categories, but patterns of onset and evolvement of impairment of vibration sensitivity were less clear than with grip and pinch strength.

Conclusions: Persistent, mainly motor, impairment of the peripheral nervous system was found in men two years after OP poisoning, in particular in severe occupational and intentional poisonings with neuropathic OPs. This finding is possibly due to remaining organophosphate induced delayed polyneuropathy.

The frequent use of the highly toxic organophosphate insecticides (OPs) in Nicaragua and in many other developing countries is an important cause of occupational illness.[1] Moreover, OPs are a common vehicle for suicide attempts,[2] which generally result in more severe poisonings than accidental occupational poisonings.[3]

Acute toxic signs and symptoms after poisonings with OPs result from the inhibition of the acetylcholinesterase enzyme in both the central and the peripheral nervous system.[2] Among the central nervous systems symptoms are dizziness, headache, confusion, and respiratory depression. Muscarinic effects include increased glands secretions (saliva, mucus, sweat, tears, bronchial secretions), smooth muscle dysfunction (diarrhoea, miosis, blurred vision, involuntary micturition, bradycardia). Nicotinic effects include hypertension, tachycardia, muscle fasciculation, weakness, and paralysis. The recovery from acute poisoning depends on the severity of the poisoning and on the availability of treatment, and may last from one day up to a few weeks.[4]

An organophosphate induced delayed polyneuropathy (OPIDP) has been reported after severe poisoning by some organophosphate pesticides. OPIDP is a dying back axonopathy characterised by sensory and motor symptoms that develop days to weeks after poisoning.[2] In addition to the damage in peripheral nerves, OPIDP may also involve damage to the spinal cord and medulla oblongata,[5] and symptoms of OPIDP include paresthesias in leg and arms, leg cramping and weakness, foot drop, and in severe cases paralysis of limb muscles.[2] A number of case reports and case series performed shortly after organophosphate poisoning,[6–9] and cross sectional studies performed several years after poisoning,[10 11] have reported different degrees of impairment in motor and sensory functions. Among the OPs repeatedly reported to have caused neuropathy in humans are methamidophos,[7 12 13] chlorpyrifos,[8 14] and trichlorphon.[15] It has been suggested that persistent subclinical neuropathy may be frequent.

The intermediate syndrome (IMS) has also been reported as a possible illness resulting from OP poisoning.[5 16–23] IMS generally appears between 24 and 96 hours and its symptoms are reported to last up to 18 days.[16] It has been suggested that pathogenesis of IMS involves combined pre- and postsynaptic dysfunction of neuromuscular transmission as a result of prolonged acetylcholinesterase inhibition.[18] Muscular weakness (mainly proximal limb muscles and neck flexors) and cranial nerve palsies characterise IMS.[16] Knowledge of how often OPIDP and IMS occur and the long term clinical course of OP poisonings is limited.

This is the first study to repeatedly examine a cohort of men poisoned with OPs during several years after poisoning. We have previously reported the results of hand strength and hand and foot vibration thresholds around one week and around seven weeks after poisoning.[24 25] Briefly, we found some hand weakness in both examinations in all men poisoned with OPs. However, in men with severe intentional poisoning due to OPs that have been reported to cause OPIDP, the weakness was particularly marked, and loss of strength worsened seven weeks after the poisonings.[24] In this subgroup, toe vibration thresholds were also impaired seven weeks after poisoning.[25] Some of the most severely poisoned patients actually developed clinical OPIDP. For the less severely poisoned patients we interpreted our findings as compatible with subclinical OPIDP or development of IMS. We now report the results of a third examination performed

Abbreviations: IMS, intermediate syndrome; OP, organophosphate; OPIDP, organophosphate induced delayed polyneuropathy

two years after poisoning. Sensory and motor function were quantitatively measured and related to the severity of the initial poisoning and type of OP agent that caused the poisoning, in order to determine whether there were persistent sensory or motor effects from OP poisoning after two years.

SUBJECTS AND METHODS

Subjects

Seventy one men who had been admitted for acute OP poisoning to two hospitals in the cities of León and Chinandega, Nicaragua, between 1 July 1992 and 15 December 1996, and who had survived the acute poisoning, were examined 1–18 days after poisoning at hospital discharge (median 6 days, 77% during the first 10 days). Of these poisoned patients, 59 men were re-examined around seven weeks later (18–128 days after poisoning, median 49 days, 84% between 24 and 90 days); and 48 poisoned men were examined a third time between 24 and 32 months (mean 28 months) after the poisoning. Thus, from the group initially examined, 12 poisoned men were not examined a second time and 11 additional men were not examined a third time because they were not located. Most of these men had left the country in search of better job opportunities.

Seventy four healthy male members of fishing and cattle cooperatives were selected as the comparison group and examined. Of these, 39 men were re-examined around seven weeks later; and 28 were examined a third time around two years later during approximately the same period as the poisoned group. Thirty five men in the comparison group were not located for the second examination because they had moved in search of work (27 fishermen moved to distant cooperatives, six cattle farmers to banana plantations, and two cattle farmers had left the country). After two years, 11 additional men (all cattle farmers) in this group could not be located because they had moved for the same reason. Some in the comparison group had been exposed to pesticides, but none reported ever having been poisoned. Details about the selection of the study group have been previously reported.[24] Table 1 presents general characteristics of the study group.

Exposure assessment

The pesticide responsible for poisoning was determined by patient report on hospital examination and confirmed by field visits (or in one case by chemical analysis). No new poisonings occurred in the two year period between the poisonings and the third examination among any member of the study group. Self reported exposure to pesticides also decreased notably in all exposure groups during the two years following the poisonings.

Neuropathic versus non-neuropathic OPs

Thirty three poisonings by OPs, previously reported in the literature as causes of clinical OPIDP, were classified as neuropathic, namely methamidophos[12 13] with 16 occupational and four intentional poisonings, chlorpyrifos[8 14] with 12 occupational poisonings, and fenthion[23] with one occupational poisoning. Of the 15 poisonings with OPs regarded as ''non-neuropathic'', all of them occupational, six were due to edifenphos, four to methyl parathion, two to phorate, two to malathion, and one to terbufos.

Severity of the poisoning

Signs and symptoms were obtained through a standardised clinical examination and interview performed by a medical doctor at the time of hospital admission. Copies of the hospital records for every poisoned subject were obtained. Poisoning severity was classified as mild, moderate, or severe according to a predefined list of sign and symptoms and, in one case, a very low acetylcholinesterase activity, as described previously.[24 25] None of the poisonings was classified as mild. The nature of the poisoning was a further measure of severity applied to the severe poisonings with ''neuropathic'' OPs. Information on the nature of poisoning was obtained from the medical records. Among participants in the third examination were four intentional and 44 occupational poisonings.

Confounders

Information concerning potential confounders was obtained from a standardised interview performed at each examination. Potential confounders considered were age (in years); formal educational level (less than four years and four or more years); lifetime occupational exposure to OPs (divided into none, low, and high, according to the median exposure (32 days) among those exposed to these pesticides), alcohol consumption (categorised as none, low, or high according to median alcohol consumption (400 g/month) among those who did drink alcohol); and body mass index (weight in kg/height in m^2), categorised as low or high according to the median.[8 21] Other potential confounders such as exposure to lead, and intake of medicines with suspected adverse effects on the nervous system were investigated through questionnaire, but none of the participants were exposed to these, nor had a history of diseases associated with neuropathy. More

Table 1 General characteristics of the study population

	Controls (n = 28)	Poisoned with non-neuropathic OPs (n = 15)	Moderately poisoned with neuropathic OPs (n = 19)	Severely poisoned with neuropathic OPs (n = 14)
Age (median, range), y	30.3 (17–51)	19.5 (14–39)	22.5 (15–64)	23 (15–62)
Education (median, range), y	4.0 (0–10)	6 (0–8)	4 (0–9)	3 (0–9)
Occupation, n (%)				
Agriculture	0	14 (93)	16 (84)	13 (93)
Cattle farming	1 (4)	0	0	0
Fishing	27 (96)	0	0	0
Other	0	1 (7)	3 (16)	1 (7)
Long term OP exposure, n (%)*				
None	18 (64)	7 (47)	9 (48)	7 (50)
Low (<32 days)	6 (22)	5 (33)	5 (26)	5 (36)
High (>32 days)	4 (14)	3 (20)	5 (26)	2 (14)
Alcohol consumption, n (%)†				
None	10 (36)	7 (47)	7 (37)	5 (36)
Low (< median)	5 (18)	5 (33)	9 (47)	5 (36)
High (> median)	13 (46)	3 (20)	3 (16)	4 (28)
Body mass index	22.1 (2.7)	22.6 (2.6)	22.0 (3.7)	21.4 (4.1)

*Median 32 days.
† Median 411.3 g/month.

detailed information on potential confounders was included in the previous reports.[24 25]

Testing

The examinations were carried out at the university hospital of the city of León. The participants signed an informed consent with each examination session, and they were reimbursed for expenses and lost wages on the examination days. Grip and pinch strength measurements were performed according to a previously recommended standardised procedure using an adjustable handle Jamar dynamometer and the B & L Engineering pinch gauge, respectively.[26 27] Pinch strength was examined using key (thumb pad to lateral aspect of middle phalanx of index finger) and palmar (thumb pad to pads of index and middle finger) modalities.[26 27] The mean of three successive trials was used as the outcome for each strength modality. Since palmar pinch strength yielded similar results to key pinch, only the results of the latter test will be shown.

Vibration thresholds were measured using a Vibraton II (Sensortek, Inc., Clifton, NJ) for dominant index and big toe.[28] Five readings (trials) were made for each finger and toe. The first, the lowest, and the highest readings of vibrametry were discarded. The outcome used was the average of the remaining two readings (X) after conversion into microns of vibration amplitude (A) through the formulae A = K*(X)**2.05, where K is a constant that represents the peak to peak displacement of the stimulator post. The room temperature in which the examinations were performed was 29–32°C at the first examination, 28–33°C at the second examination, as previously reported,[24 25] and 29–33°C at the third examination.

Statistical analysis

The index finger and big toe vibration threshold distributions were normalised with log transformation of the amplitude (log microns).[28] Since grip and pinch strengths (kg) were symmetrically distributed, no transformation was needed. Seventy two linear multiple regressions were run, for each of the above four dependent (effect) variables at each of the three time points (at discharge, 7 weeks, and 2 years) and for each six exposure contrasts coded as the following binary variables:

- Moderate poisoning with non-neuropathic OPs. 0: No (controls); 1: Yes
- Severe poisoning with non-neuropathic OPs. 0: No (controls); 1: Yes
- Moderate poisoning with neuropathic OPs. 0: No (controls); 1: Yes
- Severe poisoning with neuropathic OPs. 0: No (controls); 1: Yes.

The analyses were based on the subjects who participated in all examinations (48 poisoned, 28 controls), but the numbers in the analyses varied, as each analysis excluded a poisoning subgroup. Age (in years) was added to each model as a potential confounder, after the preliminary analyses indicated that the other potential confounders altered the coefficients for the exposure variables only minimally. The regression coefficient of the binary variables indicates the mean difference between the exposure group (as indicated by 1) and the controls (0).

In addition to these 48 models, a further set of 32 models were run, using individual changes between the third and first and between the third and second examinations in log of finger and toe vibration threshold and grip and pinch strength as dependent variables. The regressors were as above, and age was included. SPSS for Windows v. 8.0 was used. A regression coefficient with $p<0.05$ was considered significant.

Additional analyses were done to evaluate the potential selection bias due to attrition, by comparing the test scores of subjects who participated only in examination I with those who had both the first and second examination, and by comparing the test scores of those who participated only in examinations I and II with those who participated in all three examinations.

RESULTS

As reported earlier, grip and pinch strength of men poisoned with "non-neuropathic" OPs were slightly but not significantly lower than in the controls at examination I (at hospital discharge) and at examination II (about seven weeks later).[24] At the time of examination III (two years after the poisoning), grip strength had recovered and was not different from controls. However, pinch strength, remained lower than for controls both for moderately and severely poisoned subjects (table 2).

Among the men with poisonings with neuropathic OPs, those with moderate poisonings showed an evolution similar to the subjects poisoned with non-neuropathic OPs. In men with severe poisonings with neuropathic OPs, we had reported large and significant deficits in grip and pinch strength at examination I, which worsened considerably at the second examination, in particular in the subset of severe intentional poisonings.[24] Although also these men recovered part of their strength at examination III, especially grip strength, they remained significantly weaker than the controls (table 2). Further stratification of the subjects severely poisoned with neuropathic OPs into occupational and intentional poisonings, showed the largest weakness in the subset of subjects with severe intentional poisonings (regression coefficient grip strength −8.8 for intentional versus −6.8 for occupational, and regression coefficient pinch strength −2.0 for intentional versus −1.5 for occupational, all significant). The intra-individual mean changes in grip and pinch strength between examinations were not significantly different from the controls, but revealed that the steep decrease in strength observed between the first and second examination for the severely poisoned subgroup with neuropathic OP, was followed by some strength increase for this same group between the second and the third examination.

With regard to the vibrometry results at examinations I and II, there was a significant increase for the big toe vibration threshold among subjects with severe intentional poisonings with neuropathic OPs, but the thresholds at examinations I and II did not follow such a clear pattern of impairment as we observed for hand strength.[25] However, at examination III, the thresholds for index finger and big toe were somewhat higher than in the controls for all categories of OP poisoned, significant for the index finger threshold of the subjects with severe neuropathic poisoning (table 3). At stratification of the severe poisonings with neuropathic OPs into occupational and intentional poisonings, the high big toe vibration thresholds observed at examination II for severe intentional poisonings disappeared (data not shown). The intra-individual threshold mean changes in the index finger and big toe vibrometry between examinations were not significantly different from the controls, but they revealed increases in big toe and index finger thresholds between the first and third examination for the severely poisoned subgroup with neuropathic OPs.

Results of analyses restricted to those whose examination I was performed less than 10 days after poisoning were similar to the results for the larger sample for both strength and vibration threshold (data not shown). Results of hand strength were in general not very different among individuals of each group who did not participate in examinations II or III compared to the results for those who remained in the study (table 4). The two subjects with severe (intentional) poisoning with neuropathic OPs who dropped out at

Table 2 Comparison of grip and pinch strength (kg) between individuals poisoned with OPs and control subjects

	Grip strength			Pinch strength		
	1st	2nd	3rd	1st	2nd	3rd
Controls (n = 28)						
Mean (SD)	44.0 (6.2)	45.9 (6.6)	47.1 (6.3)	9.7 (2.1)	9.9 (1.9)	10.4 (1.8)
Poisoned with non-neuropathic OPs						
Moderate poisoning (n = 10)						
Mean (SD)	41.7 (8.3)	42.6 (6.3)	47.3 (7.1)	9.0 (1.5)	9.6 (1.4)	9.7 (1.9)
Adjusted difference (95% CI)	−2.2 (−8.1 to 3.7)	−3.1 (−8.2 to 2.0)	−0.3 (−5.2 to 4.6)	−0.6 (−2.0 to 0.9)	−0.2 (−1.7 to 1.3)	−0.8 (−2.0 to 0.4)
Severe poisoning (n = 5)						
Mean (SD)	39.3 (12.5)	40.3 (8.9)	47.6 (4.7)	9.4 (2.8)	9.2 (1.4)	9.4 (0.6)
Adjusted difference (95% CI)	−4.7 (−12.3 to 3.0)	−5.6 (−12.3 to 1.0)	0.5 (−5.9 to 6.9)	−0.3 (−2.2 to 1.6)	−0.6 (−2.6 to 1.3)	−1.0 (−2.5 to 0.6)
Poisoned with neuropathic OPs						
Moderate poisoning (n = 19)						
Mean (SD)	41.0 (7.8)	43.5 (6.4)	46.0 (8.1)	9.2 (1.7)	9.5 (2.1)	9.9 (1.8)
Difference (95% CI)	−3.0 (−7.8 to 1.7)	−2.6 (−6.8 to 1.6)	−0.8 (−4.8 to 3.1)	−0.6 (−1.8 to 0.6)	−0.4 (−1.6 to 0.8)	−0.4 (−1.4 to 0.5)
Severe poisoning (n = 14)						
Mean (SD)	34.5 (8.6)	33.8 (7.4)	39.6 (5.5)	8.4 (2.0)	7.8 (2.4)	8.7 (0.8)
Difference (95% CI)	−9.6 (−14.7 to −4.5)	−12.1 (−16.6 to −7.7)	−7.1 (−11.4 to −2.9)	−1.4 (−2.7 to −0.2)	−2.0 (−3.3 to −0.8)	−1.6 (−2.6 to −0.6)

Results expressed as mean and standard deviation (SD), age adjusted regression coefficient (RC) with 95% confidence intervals (CI).

examination III, had considerably higher vibration thresholds at the time of examination II than those who remained in the study (table 4).

DISCUSSION

This is the first study reported in the scientific literature that systematically follows a group of OP poisoned subjects for several years. The main objective of this study was to evaluate the association of OP poisoning with chronic peripheral nervous system impairment.

Our main finding was persistently diminished hand strength two years after poisoning in men with previous occupational and intentional poisonings with neuropathic OPs. Vibration thresholds were slightly increased after the two year period among all OP poisonings, the index finger vibration thresholds being significantly worse for men with severe poisonings with neuropathic OPs.

In a previous evaluation of the same study group, based on examinations shortly after the recovery from the acute OP poisoning episode and around seven weeks later[24] we found muscle weakness that was present at the time of hospital discharge. Motor impairment, which was more evident in men with neuropathic OP poisonings, persisted, and in the most severe cases, worsened a few weeks later. In that study, men with poisonings with non-neuropathic OPs and men with moderate poisonings with neuropathic OPs also had a modest decrease in hand strength during the first two examinations, which is compatible with a mild OPIDP. We observed here that these subgroups recovered substantially after two years, which agrees with the evolution of OPIDP.[5] It is possible that decreased strength found at examination I among those with intentional poisonings may have been due to psychological factors associated with underlying depression. However, this explanation seems unlikely since all those poisoned (including those with intentional poisoning) improved over time, and there was no difference in the results between occupational and intentional poisonings at hospital discharge. Persistent inhibition of acetylcholinesterase is a possible explanation for the early finding of motor

Table 3 Comparison of vibration thresholds (log microns) between individuals poisoned with OPs and control subjects

	Index finger			Big toe		
	I	II	III	I	II	III (29)
Controls (n = 28)						
Mean (SD)	0.08 (0.27)	0.07 (0.25)	0.04 (0.21)	0.51 (0.33)	0.51 (0.22)	0.55 (0.26)
Poisoned with non-neuropathic OPs						
Moderate poisoning (n = 10)						
Mean (SD)	0.02 (0.36)	0.01(0.28)	0.08 (0.35)	0.47 (0.34)	0.49 (0.16)	0.56 (0.32)
Difference (95% CI)	−0.02 (−0.26 to 0.22)	−0.04 (−0.21 to 0.14)	0.08 (−0.12 to 0.28)	0.00 (−0.23 to 0.24)	0.04 (−0.20 to 0.28)	0.06 (−0.16 to 0.27)
Severe poisoning (n = 5)						
Mean (SD)	0.11 (0.33)	0.02 (0.26)	0.12 (0.14)	0.60 (0.22)	0.67 (0.34)	0.70 (0.28)
Difference (95% CI)	0.04 (−0.28 to 0.35)	−0.05 (−0.27 to 0.18)	0.10 (−0.16 to 0.37)	0.10 (−0.20 to 0.41)	0.18 (−0.13 to 0.49)	0.16 (−0.12 to 0.43)
Poisoned with neuropathic OPs						
Moderate poisoning (n = 18)						
Mean (SD)	0.18 (0.43)	0.10 (0.24)	0.16 (0.25)	0.64 (0.35)	0.56 (0.41)	0.67 (0.21)
RC (95% CI)	0.09 (−0.11 to 0.28)	0.02 (−0.12 to 0.17)	0.10 (−0.05 to 0.26)	0.12 (−0.07 to 0.31)	0.04 (−0.15 to 0.23)	0.11 (−0.06 to 0.28)
Severe poisoning (n = 14)						
Mean (SD)	0.16 (0.24)	0.10 (0.14)	0.21 (0.28)	0.59 (0.29)	0.61 (0.48)	0.70 (0.43)
RC (95% CI)	0.07 (−0.14 to 0.17)	0.02 (−0.14 to 0.17)	0.19 (0.01 to 0.36)	0.07 (−0.14 to 0.27)	0.09 (−0.12 to 0.30)	0.13 (−0.06 to 0.32)

Results expressed as mean and standard deviation (SD), age adjusted regression coefficient (RC), with 95% confidence intervals (CI).

Table 4 Comparison of grip strength, pinch strength, index finger vibration thresholds, and big toe vibration thresholds among subjects who left the study and those who remained

	Examination I		Examination II	
	Participants who had both examinations I and II	Participants who only had examination I	Participants with all 3 examinations	Participants who only had examinations I and II
Grip strength (kg)				
Controls	43.2 (5.9) (n = 39)	43.9 (6.0) (n = 35)	45.9 (6.6) (n = 28)	43.9 (6.0) (n = 11)
Poisonings with ''non-neuropathic'' OPs	40.2 (9.0) (n = 18)	41.0 (7.5) (n = 6)	41.8 (7.0) (n = 15)	41.3 (5.7) (n = 3)
Moderate poisonings with ''neuropathic'' OPs	39.2 (7.4) (n = 25)	39.9 (6.3) (n = 2)	43.5 (6.4) (n = 19)	41.0 (7.0) (n = 6)
Severe poisonings with ''neuropathic'' OPs	34.4 (8.4) (n = 16)	35.0 (7.0) (n = 4)	33.8 (7.4) (n = 14)	34.0 (6.2) (n = 2)
Pinch strength (kg)				
Controls	9.9 (1.5) (n = 39)	9.8 (1.5) (n = 35)	9.9 (1.9) (n = 28)	9.9 (1.7) (n = 11)
Poisonings with ''non-neuropathic'' OPs	9.2 (1.8) (n = 18)	9.4 (1.3) (n = 6)	9.5 (1.3) (n = 15)	9.5 (1.4) (n = 3)
Moderate poisonings with ''neuropathic'' OPs	9.0 (1.7) (n = 23)	9.1 (1.7) (n = 4)	9.5 (2.1) (n = 19)	9.3 (1.2) (n = 4)
Severe poisonings with ''neuropathic'' OPs	8.3 (2.0) (n = 16)	8.0 (2.1) (n = 4)	7.8 (2.4) (n = 14)	7.7 (2.0) (n = 2)
Index finger vibration thresholds (log microns)				
Controls	0.13 (0.26) (n = 39)	0.09 (0.20) (n = 35)	0.07 (0.25) (n = 28)	0.09 (0.24) (n = 11)
Poisonings with ''non-neuropathic'' OPs	0.04 (0.35) (n = 18)	0.01 (0.32) (n = 6)	0.10 (0.23) (n = 15)	0.01 (0.30) (n = 3)
Moderate poisonings with ''neuropathic'' OPs	0.19 (0.38) (n = 23)	0.15 (0.33) (n = 4)	0.10 (0.24) (n = 18)	0.12 (0.27) (n = 5)
Severe poisonings with ''neuropathic'' OPs	0.16 (0.23) (n = 16)	0.16 (0.16) (n = 4)	0.10 (0.14) (n = 14)	0.44 (0.31) (n = 2)
Big toe vibration thresholds (log microns)				
Controls	0.60 (0.35) (n = 39)	0.55 (0.31) (n = 35)	0.51 (0.22) (n = 28)	0.52 (0.26) (n = 11)
Poisonings with ''non-neuropathic'' OPs	0.52 (0.31) (n = 18)	0.47 (0.21) (n = 6)	0.55 (0.41) (n = 15)	0.48 (0.20) (n = 3)
Moderate poisonings with ''neuropathic'' OPs	0.65 (0.32) (n = 23)	0.61 (0.30) (n = 4)	0.56 (0.41) (n = 18)	0.55 (0.39) (n = 5)
Severe poisonings with ''neuropathic'' OPs	0.57 (0.30) (n = 16)	0.58 (0.43) (n = 4)	0.61 (0.48) (n = 14)	1,15 (0.10) (n = 2)

Results expressed as mean (SD).

effect at the first examination, but persistent inhibition could not explain the long term persistence of motor effects, because this enzyme recovers with time corresponding to clinical improvement, as we have discussed previously.[24 25] We have reported impaired vibrotactile thresholds in the big toe of men with severe intentional poisonings with neuropathic OPs seven weeks earlier,[25] which is compatible with neurological impairment primarily affecting the distal portion of the inferior extremities in OPIDP.[5]

The persistent weakness and increased index finger and toe vibration thresholds two years after severe poisoning with neuropathic OPs (both occupational and intentional), are compatible with the development of neuropathy and in accordance with reports based on clinical examinations and with cross sectional epidemiological studies. De Jager and colleagues[29] found weakness of distal muscles in a case of OPIDP one year after an OP poisoning. In a case studied by Stamboulis and colleagues,[30] similar findings were reported. Vacilescu and colleagues[31] observed residual distal weakness in two cases of OP poisoning that had occurred 18 months earlier. Most OPIDP signs regressed after 18 months in a case reported by Jedrzejowska and colleagues,[32] but distal spastic paralysis persisted three years later, supportive of damage to the long axons of peripheral nerves and long tracts in the spinal cord following a ''dying back pattern''. For tri-ortho-cresyl-phosphate (TOCP), a non-pesticide OP, it has been suggested that motor neuropathy associated with OPIDP may be particularly persistent.[33] Savage and colleagues[10] found some evidence of motor impairment in individuals examined around nine years after OP poisoning. Steenland and colleagues reported increased finger and toe vibration thresholds among individuals poisoned several years before with OPs.[34] McConnell and colleagues also reported increased vibration thresholds among men with a history of OP poisonings on average 22 months earlier.[11] Although OPIDP has both a motor and a sensory component, in clinical reports motor impairment seems to be a more dominant feature. We looked at our data to see whether there was a correlation between motor and sensory impairment, but at each of the examinations, age adjusted correlation coefficients, although in general in the expected negative direction, were mostly low and non-significant (for example, correlations between grip strength and big toe vibration thresholds between −0.04 and 0.45). Although there are other mechanisms of OP toxicity that could explain persistent weakness two years after poisoning, among them muscle necrosis due to prolonged stimulation[35 36] or excess of calcium in nerve endings that leads to localised muscle injury,[37] the overall picture of occurrence and evolution of strength and sensory impairment points, in our opinion, to OPIDP.

Our positive findings among those individuals poisoned with non-neuropathic OPs may not be so surprising in the light of increasingly reported effects on the peripheral nervous system caused by these pesticides. De Bleeker and colleagues[18] and Shailesh and colleagues[19] reported IMS in six and 26 cases respectively of poisoning with ethyl-parathion and/or methyl-parathion; Samuel and colleagues[20] reported 33 cases of IMS among individuals poisoned with quinalophos, methyl-parathion, phosphomidon, monocrotophos, malathion, and dimethoate; and Benslama and colleagues[22] reported a case of IMS due to malathion.

The results of this study may have been affected by various systematic errors. It is possible that previous long term exposure to ''neuropathic'' OPs (or to non-neuropathic OPs) could have resulted in chronic peripheral nervous system impairment. Cole and colleagues reported reduced muscle power and increased vibration thresholds in 144 subjects exposed to pesticides including OPs.[38] However, in our study long term exposure evaluated retrospectively by questionnaire was not found to confound our results. In a study of 164 pesticide applicators in South Africa, long term exposure to OPs did not result in a neuropathic effect.[39]

The suitability of the control group in terms of similar educational level and socioeconomic background was confirmed in the interviews. However, the controls were older on average and had higher alcohol consumption. Age was controlled for in the analyses, but any residual confounding would be in the direction of overestimation of effects. Conversely, more alcohol intake among the controls would have reduced the differences, but alcohol did not appear to be a confounder in our data. The five subjects among those poisoned in non-agricultural occupations may have had a lower baseline strength than the controls, possibly causing some bias towards overestimation of the effect. However, the

vast majority of the poisoned subjects were employed in agriculture (90%), involving long term heavy physical work similar to the controls. Specifically in the group of those severely poisoned with neuropathic OPs, it is unlikely that individuals had lower hand strength as a consequence of lack of physical training. All of them, including those with intentional poisonings, had returned to heavy physical work by examination III.

We did not get any information that non-participation in examinations II or III was related to health. Rather non-participation was due to migration related to high unemployment rates in Nicaragua. It is likely that the most healthy persons are more inclined to migrate for better job opportunities. Loss to follow up did not seem to have altered the results for most of the comparisons. No important differences were found in vibrometry or hand strength mean values in the first and second examination between those individuals in the exposed group or in the control group who did not participate in the third examination compared to those who remained in the study. The only exception was the loss of two poisoned in the very small group of severe intentional poisonings with neuropathic OPs who had very high thresholds at the second examination compared to those who remained for the third examination. It is possible that, had they been examined at the third test occasion, we would have observed a higher mean vibration threshold in this subgroup. As a final point, the likelihood of misclassification of the pesticides as neuropathic or non-neuropathic seems low given the high correspondence between the statements in the emergency room and the field confirmations that validated our classification of the poisonings.[24]

In conclusion, is likely that the findings of the present study among those men severely poisoned with ''neuropathic'' OPs reflect the development of sensory-motor OPIDP and its residual effects. In men poisoned with OPs previously considered as non-neuropathic or with moderate poisonings with neuropathic OPs there are effects on hand strength which last for at least several months but have resolved after two years.

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Authors' affiliations

J Miranda, E Delgado, Department of Preventive Medicine, National Autonomous University, León, Nicaragua (UNAN)
I Lundberg, Division of Occupational Health, Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
R McConnell, Department of Preventive Medicine, University of Southern California, Los Angeles, USA
R Cuadra, Department of Internal Medicine, National Autonomous University, León, Nicaragua (UNAN)
C Wesseling, Central American Institute for Studies on Toxic Substances (IRET), Universidad Nacional, Heredia, Costa Rica (UNA)
M Keifer, International Scholars in Occupational and Environmental Health, University of Washington, Seattle, USA

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