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Parkinsonism signs and symptoms in agricultural pesticide handlers in Washington State

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Abstract

Objectives—Examine associations between pesticide exposure and signs or symptoms of parkinsonism.

Methods—Prior to the 2014 pesticide spray season we examined 38 active pesticide handlers age 35-65 (median 43.5) who participated in the State of Washington's cholinesterase monitoring program in the Yakima Valley, where cholinesterase-inhibiting insecticides are applied in fruit orchards. A movement disorders specialist assessed the workers using the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore 3 (UPDRS3). Participants also self-reported work and medical histories, including the UPDRS activities of daily living subscore 2 (UPDRS2). We explored the relation between these scores and lifetime occupational pesticide exposure while accounting for age.

Results—All participants were Hispanic men born in Mexico who had worked in agriculture for 4-43 years (median 21 years, including 11 years applying pesticides, mostly in the U.S.). Ten participants (26%) reported difficulty with one or more UPDRS2 activities of daily living (maximum=2) and nine (24%) had a UPDRS3>0 (maximum=10). The most common symptom and sign, respectively, were excess saliva (n=6) and action tremor (n=5). UPDRS2 and UPDRS3 scores were unrelated to the number of years applying pesticides, but UPDRS3, especially action tremor, was positively associated with living on or by a farm.

Conclusions—Symptoms and signs of parkinsonism were absent to mild in this small sample of active workers who apply cholinesterase-inhibiting insecticides in Washington State, U.S. Future

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studies should be larger, and examine older, retired workers with greater cumulative exposure to agricultural pesticides at work and home, including other types of agricultural pesticides.

Keywords

Cholinesterase Inhibitors; Occupational Health; Parkinsonian Disorders; Parkinson Disease; Pesticides

1. Introduction

Parkinsonism (PS) is a relatively common movement disorder characterized by rigidity, bradykinesia, tremor and postural instability. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a chemical that is structurally similar to the herbicide paraquat, causes PS in humans.[1] Animal models of PS that employ MPTP, paraquat, the insecticide rotenone, and the fungicide maneb indicate that oxidative stress is the underlying mechanism,[2] suggesting that a variety of pesticides, including more commonly used pesticides, may contribute to PS. This includes the insecticide chlorpyrifos, which may increase α-synuclein or its aggregation in neurons.[3] α-synuclein is the hallmark protein of the most common cause of PS, Parkinson disease (PD). Occupational exposure to pesticides is associated with an approximately 50% increased risk of PD.[4,5] However, epidemiologic evidence for associations between PD and specific pesticides, including chlorpyrifos, is mixed.[6-9] One challenge is that PD is uncommon, especially in working age individuals. However, because PD likely develops over the course of many years, signs and symptoms of PS may be apparent long before diagnosis. Studies in which pesticide-exposed workers have been examined for signs of PS have been limited to workers exposed to paraquat[10] or maneb.[11] In this study, we examined agricultural pesticide handlers from apple orchards in central Washington State, where insecticides such as chlorpyrifos are much more commonly used.[12] We hypothesized that we might observe parkinsonian symptoms and signs even in a contemporary sample of active workers, as has been observed for workers exposed to maneb[11] or other sources of manganese.[13]

2. Materials and Methods

2.1 Study participants

All study participants provided oral informed consent, and the University of Washington Institutional Review Board approved all study procedures, prior to contact with any workers potentially eligible for the present study. All recruitment materials and study protocols were designed to minimize any potential effects of difficulty speaking English or reading Spanish on subject recruitment or participation. Notably, the screening and recruitment script (read out loud) was written at a seventh grade reading level, and the informed consent form was written at a fifth grade reading level. In addition, bilingual recruitment staff (M.N., P.P.) offered to read study materials in English or Spanish to all potential participants during the recruitment process.

In order to have a defined population and ensure that most participants had substantial exposure to agricultural pesticides such as chlorpyrifos, eligibility requirements included: 1) work in the coming season as a pesticide handler in a fruit orchard, and 2) current participation in the State of Washington's Cholinesterase Monitoring Program. This statewide monitoring program[14] is an annual, mandatory (opt out) program that obtains pre-spray-season blood from approximately 90% of all pesticide applicators in the state who anticipate applying cholinesterase inhibiting insecticides for >30 hours in any 30 day period that year. We also required participants to be 35-65 years of age to focus on active workers with pesticide exposures of sufficient duration to be potentially related to the development of PS signs and symptoms.

We identified workers who met the above eligibility criteria at their baseline (pre-spray-season) visits to one of two clinics among the clinics participating in the statewide monitoring program, The Healthy Worker and the Central Washington Occupational Medicine clinics, in Yakima. In February and March 2014, study staff (M.N., P.P.) screened 238 potential participants from 20 worksites; 99 were ineligible, most because they were <35 years of age. Of the remaining 139 eligible workers, 70 (50%) agreed to participate. Each participant was scheduled for an exam with a neurologist specializing in movement disorders (S-C. H.) on one of two Saturdays in March at the Yakima offices of the Pacific Northwest Agricultural Safety and Health Center. Thirty-eight (54%) of enrolled participants came to the exam scheduled with the study neurologist. Most participants who were scheduled on the first Saturday attended, whereas most scheduled on the second Saturday did not. Several enrolled participants who were scheduled for the second Saturday but unable to come to their examination appointment volunteered that they were unable to come because they were asked to work that day applying pesticides due to unexpectedly warm weather and low wind.

2.2 Assessment of agricultural pesticide exposure

At the time of enrollment each participant also received a structured questionnaire on medical and agricultural work histories to complete at home in Spanish. We wrote the questionnaire at a fifth grade reading level, and multiple pages of the questionnaire stated that participants could ask for help in completing it. Bilingual staff (M.N., P.P.) were also available to help participants complete the questionnaire on the day of the exam.

We assessed agricultural pesticide exposure through the take-home questionnaire. Because PS often takes many years to develop, we focused on cumulative occupational pesticide exposure, rather than recent or acute exposures. Specifically, the questionnaire ascertained the number of years working “at orchards, vineyards, greenhouses and farms that grow crops such as food or flowers” (hereafter “farm”) and the number of years they had applied pesticides. Participants also reported the countries of exposure, main crops and use of personal protective equipment (PPE). All participants completed this questionnaire prior to the exam.

2.3 Assessment of parkinsonian symptoms and medical history

The structured take-home questionnaire included all questions from the validated Spanish language version of Unified Parkinson's Disease Rating Scale (UPDRS)[15] activities of daily living subscore 2 (UPDRS2) questionnaire. In active workers we anticipated minimal difficulties with activities of daily living (few if any scores >1) and therefore assessed each of these in a simplified yes/no (score 0 vs. 1-4) format. The questionnaire also inquired about constipation in the past week, hyposmia and REM sleep behavior disorder (RBD), non-motor conditions associated with PD that may occur prior to PD diagnosis.[16] We used simplified questions based on more extensive batteries.[17,18] Responses to these questions and the UPDRS2 questionnaire we hereafter refer to as “symptoms” of PS.

The questionnaire also inquired about past and current tobacco use, caffeine consumption, family history of PD and personal history of medication use and conditions relevant to the assessment of PS. These included musculoskeletal disorders (arthritis, bone fracture and spinal injury) and vascular co-morbidities (stroke, hypertension, heart disease and diabetes) that could affect the UPDRS3 score.

2.4 Assessment of parkinsonism and parkinsonian signs

A neurologist experienced in movement disorders (S-C. H.) conducted all exams in person with the assistance of a certified interpreter (P.P.). The study neurologist assessed participants for signs of PS, including the UPDRS motor subscale 3 (UPDRS3). This has been applied previously to worker cohorts as described elsewhere,[13] and ascertains a variety of PS signs such as tremor, postural instability, rigidity, bradykinesia, and abnormalities in gait, speech and expression. The neurologistalso classified participants as having PD, another type of PS, or neither. The neurologist remainedblinded to the participant's work history for the duration of the exam.

2.5 Statistical analysis

We used Stata version 11 (College Station, TX) to assess the relation between cumulative agricultural pesticide exposure and PS symptoms and signs. Because we sampled participants from an actively working population that is unlikely to exhibit severe symptoms and signs of PS we dichotomized health outcomes: any vs. no self-report of symptoms (hyposmia, RBD, constipation or difficulty with UPDRS2 activities of daily living); any vs. no neurologist assessed signs of PS (UPDRS3>0); and any vs. no symptoms and/or signs. Our primary exposure variable of interest was total years applying agricultural pesticides, but we also considered total years working on a farm, because some pesticide exposure while working on a farm is likely. We used unconditional logistic regression to assess the association between PS outcomes and pesticide exposure in order to adjust for age. We verified that models were not influenced (>10%) by inclusion of current or past tobacco use, regular consumption of caffeinated drinks, or residential proximity to a farm.

3. Results

3.1 Characteristics of participants

Participants ranged in age from 35 to 65 years (median 43.5; mean 45.3, standard deviation 7.7 years). All were Hispanic Caucasian men born in Mexico. They had arrived in the U.S. at a median age of 20. Only eight (21%) participants had ever regularly used tobacco products, whereas most (89%) drank caffeinated coffee, tea or cola. None of the participants reported a family history of PD.

Participants had worked on a farm for 4 to 41 years (median 21 years). Workers had applied agricultural pesticides for up to 41 years (median 11 years). All but one worker had applied agricultural pesticides for at least one prior spray season. Only three workers had ever applied pesticides outside the US, and 86% of workers reported usually or always wearing PPE. Most worked in apple orchards, some in combination with pears, cherries or peaches. Only six (16%) of participants lived on or by a farm. The remainder lived >1 mile from a farm, most (73%) "in town."

3.2 Occurrence of parkinsonian symptoms

When we considered workers' responses to the questionnaire, i.e. self report of symptoms, 13 workers (34%) reported possibly being affected by symptoms of PS/PD (Table 1). Ten workers (26%) reported that in the past week they had difficulty with any of the 11 UPDRS2 activities of daily living. However, no worker reported having difficulty with >2 activities, and the mean simplified UPDRS2 score was only 0.29 (standard deviation 0.52). The most commonly reported symptom from the UPDRS2 questionnaire was having too much saliva when awake or asleep (n = 6 participants, 16%). Difficulty with swallowing (n = 1), speech (n = 1) or getting out of bed (n = 3) were also noted on the UPDRS2 questionnaire. Six workers (3 with UPDRS2>0; 3 with UPDRS2=0) reported one or more of the following three potential symptoms of PD: constipation in the past week, RBD or problems with sense of smell. The presence of one or more of these symptoms was associated with too much saliva (Fisher's exact p = 0.04).

3.3 Occurrence of parkinsonian signs

Based on neurologist observation of PS/PD signs, nine participants (24%) had at least one sign of PS, that is a neurologist-assessed UPDRS3 score > 0 (Table 1). The maximum was 10, and the mean was 0.76 (standard deviation 1.95). The most common sign was action tremor, which affected five participants (13%). All five had mild bilateral action tremor, likely enhanced physiological tremor or essential tremor. No participants had rest tremor or difficulties with speech, expression, arising from a chair, gait or postural instability. Four participants (11%) had some motor slowness (non-zero score on measures of bradykinesia), although only one was definitive enough to be deemed to have true bradykinesia. Only one worker had rigidity, which was mild. The study neurologist classified none of the 38 workers as having PD or definite PS based on the exam.

3.4 Predictors of parkinsonian symptoms and signs

Only half of the workers had any signs or symptoms of PS, and only three (8%) had both (Table 1). There was no indication that having either or both was less common among never tobacco users than ever tobacco users (all age-adjusted odds ratios > 1.0, data not shown in tables). Likewise there was no suggestion that PS symptoms/signs were positively associated with the number of years applying agricultural pesticides on a farm among the 34 participants with complete work history data (Table 2). PS symptoms and especially signs were weakly associated with the number of years working on a farm, but this possible association was not statistically significant (all age-adjusted p-values > 0.21).

Among the full sample of 38 workers, poor adherence to use of personal protective equipment (n = 5) or frequent same-day re-entry of pesticide treated areas (n = 9) were not positively associated with PS symptoms or signs. However, residence on or by a farm (n = 6) was associated with having any PS signs observed by the neurologist, and with action tremor in particular (all age-adjusted logistic regression p-values and two-sided Fisher's exact p-values = 0.02).

4. Discussion

Our study is one of the few in which workers exposed to pesticides have been systematically examined for signs of PS. Examination by a movement disorders specialist is a key strength of this study because some signs of PS, such as rigidity, are difficult for other clinicians to assess and would not likely be well-reported by study participants themselves. Previous studies have examined 12 paraquat-exposed workers[10] and 50 maneb-exposed workers.[11] Because the 38 workers in our study applied pesticides in apple orchards in Washington State these workers potentially had some exposure to both the herbicide paraquat and mancozeb,[12] a fungicide similar to maneb that contains the neurotoxicant manganese. However, fewer than a fifth of apple acres in this region are treated with these pesticides. As indicated by our inclusion criteria, it is more certain that these workers were exposed to cholinesterase inhibiting insecticides, such as chlorpyrifos and azinphos-methyl.[12] Some non-human studies suggest that chlorpyrifos may be relevant to PD.[3] However a recent study by our group using specimens from a similar worker group from the Yakima Valley observed no association between chlorpyrios or azinphos-methyl exposure and α-synuclein, a protein critically involved in PD.[19] The results from the present study likewise generally indicate that neither PS nor PD in particular are likely to be common in actively working agricultural pesticide handlers in this region of the US where most workers are carefully managed and monitored to help prevent over-exposure to cholinesterase inhibiting insecticides. Moreover, relatively few of our workers lived on or near a farm, where they might potentially receive additional pesticide exposure through drift or drinking water, and most reported that they usually use PPE. This is notable because the possible association between PD and paraquat in the Agricultural Health Study is confined to workers who did not use protective gloves.[20] In addition, two recent studies outside the U.S. have reported that PS may be associated with exposure to pesticides including cholinesterase inhibitors in agricultural workers, but it is essential to note that both studies relied on subject self report of PS or symptoms.[21,22]

In our small sample, a neurologist specializing in movement disorders observed no cases of definite PS, defined by >1 cardinal feature of PS, and with few exceptions UPDRS3 scores were zero or very low. The mean and standard deviation were 0.76 (1.95), which is somewhat lower than a recent study of 12 paraquat exposed workers with UPDRS3 scores of 3.5 (1.8), as might be expected given that those workers were older than ours on average (55.8 years).[10] Similarly in our study, UPDRS2 score (which captures symptoms that are common in PS but not unique to PS) was 0.29 on average (standard deviation [SD] 0.52) as compared to 0.7 (SD 0.9) in the paraquat study. Taken together these results are generally negative because of the limited extent of PS signs observed. On the other hand, Du et al. (2014)[10] conducted a brain imaging study and despite low UPDRS2 and UPDRS3 scores observed that workers exposed to pesticides (including but not limited to paraquat) had microstructural differences in the substantia nigra region of the brain when compared to age-matched subjects without occupational pesticide exposure. Those unexposed comparison workers (n = 12) had a mean UPDRS2 of 0.1 (SD 0.3), which is somewhat lower than in our sample despite being older on average (53.9 years). However, mean UPDRS3 in that sample was slightly higher at 1.0 (SD 1.7), that is, very similar to our sample, given the difference in mean age between our sample and theirs. Mean UPDRS3 was also lower in the present sample than another sample of active workers with a mean age of 51.6 years, selected for comparison to welders and with a mean UPDRS3 of 4.6 (SD 2.6).[13]

Underscoring our generally negative findings, there was no indication that symptoms or signs of PS were positively associated with total years working as a pesticide applicator, even though our inclusion criteria were designed to ensure substantial cumulative occupational pesticide exposure. The lack of association did not appear to be due to low statistical power because there was no suggestion of a positive association with years working as a pesticide applicator. Du et al. (2014)[10] likewise did not observe an association between UPDRS scores and total years exposed to pesticides. However, because applying pesticides might be difficult to do with signs of PS we cannot rule out a healthy worker survivor effect, which would most likely bias these associations down, even past null. In contrast, there was a weak positive association between total years working on a farm and PS symptoms and signs, and a significant association between living on or by a farm and PS signs. Although this association may be due to chance, it is plausible that living near the treated areas may possibly increase pesticide exposure sufficiently to affect worker health, or agricultural exposures other than pesticides could be relevant.

Our sample of workers was likely relatively unexposed to manganese, a well established neurotoxicant. Therefore, it is interesting to compare our results to those for workers exposed to the fungicide maneb and other sources of manganese. Ferraz et al. (1988) conducted neurological exams of 50 maneb-exposed workers and compared them to 19 other rural workers.[11] That study observed some action tremor and bradykinesia as observed here, but rigidity was much more common than our study. Rigidity is also common in workers exposed to manganese-containing welding fume.[13] Therefore, if non-manganese pesticides are associated with PS, the phenotype may be different than that among manganese-exposed workers. Cholinesterase inhibiting insecticides, which the present workers used, also target the human nervous system, but acute high level exposures have different observable effects than manganese. One effect of overexposure to cholinesterase inhibitors is increased saliva production.[23] This somewhat diminishes our finding that 16% of workers in our sample reported having excess saliva (sialorrhea). Otherwise this may be relatively high given that 25% of elderly (mean 80.5 years) patients without PD report sialorrhea.[24] It also was somewhat unexpected to have observed at least one person (3%) with symptoms consistent with RBD since a majority of RBD patients are diagnosed after age 50[25] and RBD only affects 0.5% of older individuals.[26]

5. Conclusions

Symptoms or signs of PS are uncommon, and if present, are negligible or mild, suggesting little to no PS, among this small sample of active agricultural workers who handle cholinesterase inhibiting insecticides in fruit orchards in this region of the US. Future studies focused on this class of pesticides should examine older workers and retirees, or workers with greater levels of exposure, such as in those living in close proximity to the treated areas and in other countries with less exposure control, to ensure that these negative findings were not due to small sample size, relatively low pesticide exposure and the healthy worker survivor effect.

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Table 1

Symptoms and signs of parkinsonism in Hispanic Caucasian men actively working as pesticide handlers in tree fruit orchards, central Washington State, March 2014

	N=38 n(%)
Any signs or symptoms of parkinsonism	19 (50)
Any symptoms	13 (34)
UPDRS2[a] > 0	10 (26)
Excess saliva	6 (16)
Difficulty getting out of bed	3 (8)
Difficulty swallowing	1 (3)
Difficulty with speech	1 (3)
Other symptoms	6 (16)
Constipation	4 (11)
Possible hyposmia	2 (5)[b]
Possible RBD	2 (5)[b]
Any signs (UPDRS3[c] > 0)	9 (24)
Action tremor	5 (13)
Motor slowness[d]	4 (11)
Rigidity	1 (3)
Both symptoms and signs	3 (8)

[a] Unified Parkinson Disease Rating Scale motor activities of daily living subscore 2, self-reported on a standardized questionnaire; difficulty with other activities of daily living not reported.

[b] One reported symptoms consistent with this condition and one was unsure whether they were experiencing these (“problems with sense of smell” or ever been told that they “sometimes make complex movements, such as waving, while you are asleep and dreaming”).

[c] Unified Parkinson Disease Rating Scale motor subscore 3, as assessed in person by a movement disorders specialist neurologist; other possible signs not observed including rest tremor, postural instability or problems with gait, expression or speech.

[d] Non-zero score on finger taps, rapid arm movements, hand movements and/or leg/foot agility; no participants had global bradykinesia scores >0; only one of these participants was deemed to have true bradykinesia.

Table 2

Signs and symptoms of parkinsonism in relation to cumulative duration of agricultural pesticide exposure among Hispanic Caucasian men actively working as pesticide handlers in tree fruit orchards (N = 34)[a], central Washington State, March 2014

	Age-adjusted odds ratio and 95% confidence interval for the presence of any parkinsonism signs and/or symptoms	
	Per year applying pesticides[b]	**Per year working on a farm[b]**
Any symptoms (UPDRS2[c]>0)	0.99 (0.92, 1.08)	1.05 (0.94, 1.18)
Any signs (UPDRS3[d]>0)	0.96 (0.87, 1.06)	1.10 (0.95, 1.28)
Any signs/symptoms (UPDRS2[c] > 0 or UPDRS3[d] > 0)	0.96 (0.89, 1.04)	1.05 (0.95, 1.16)

[a]Excludes 4/38 participants with incomplete work history data.

[b]Applying pesticides or working on a farm (orchard, vineyard, greenhouse or farm that grows crops such as food or flowers).

[c]Unified Parkinson Disease Rating Scale activities of daily living subscore 2, self-reported on a standardized questionnaire.

[d]Unified Parkinson Disease Rating Scale motor subscore 3, assessed in person by a movement disorders specialist neurologist.