Environment International 107 (2017) 75–81

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Organophosphate pesticides and *PON1* L55M in Parkinson's disease progression

Kimberly C. Paul[a], Janet S. Sinsheimer[b,c], Myles Cockburn[d], Jeff M. Bronstein[e], Yvette Bordelon[e], Beate Ritz[a,e,*]

[a] Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, USA
[b] Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, California, USA
[c] Departments of Human Genetics and Biomathematics, David Geffen School of Medicine, Los Angeles, California, USA
[d] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, CA, USA
[e] Department of Neurology, David Geffen School of Medicine, Los Angeles, California, USA

ARTICLE INFO

Keywords:
Organophosphates
PON1
Parkinson's disease
Cognitive decline
Progression

ABSTRACT

Background: Parkinson's disease (PD) has motor and non-motor features that contribute to its phenotype and functional decline. Organophosphate (OP) pesticides and *PON1* L55M, which influences OP metabolism, have been implicated in multiple mechanisms related to neuronal cell death and may influence PD symptom progression.

Objective: To investigate whether ambient agricultural OP exposure and *PON1* L55M influence the rate of motor, cognitive, and mood-related symptom progression in PD.

Methods: We followed a longitudinal cohort of 246 incident PD patients on average over 5 years (7.5 years after diagnosis), repeatedly measuring symptom progression with the Mini-Mental State Exam (MMSE), Unified Parkinson's Disease Rating Scale (UPDRS), and Geriatric Depressive Scale (GDS). OP exposures were generated with a geographic information system (GIS) based exposure assessment tool. We employed repeated-measures regression to assess associations between OP exposure and/or *PON1* L55M genotype and progression.

Results: High OP exposures were associated with faster progression of motor (UPDRS $\beta = 0.24$, 95% CI $= -0.01, 0.49$) and cognitive scores (MMSE $\beta = -0.06$, 95% CI $= -0.11, -0.01$). *PON1* 55MM was associated with faster progression of motor (UPDRS $\beta = 0.28$, 95% CI $= 0.08, 0.48$) and depressive symptoms (GDS $\beta = 0.07$; 95% CI $= 0.01, 0.13$). We also found the *PON1* L55M variant to interact with OP exposures in influencing MMSE cognitive scores ($\beta = -1.26$, 95% CI $= -2.43, -0.09$).

Conclusion: Our study provides preliminary support for the involvement of OP pesticides and PON1 in PD-related motor, cognitive, or depressive symptom progression. Future studies are needed to replicate findings and examine whether elderly populations generally are similarly impacted by pesticides or *PON1* 55M genotypes.

1. Introduction

Parkinson's disease (PD), a progressive neurodegenerative disorder with selective degeneration of dopaminergic neurons and the related motor symptoms, has many important non-motor features that contribute to its phenotype and functional decline. Cognitive impairment and neuropsychiatric symptoms are among the most prominent (Post et al., 2007). Dementia in PD patients is estimated to be as much as 2–6-fold more common than in unaffected individuals; up to 75% of PD patients who live > 10 years after diagnosis are expected to develop dementia, while depression affects up to half of all PD patients (Aarsland and Kurz, 2010). Over the course of disease, the severity and/or frequency of motor and non-motor symptoms increase and health related quality of life becomes a major concern for patients and caregivers (Santos-García and de la Fuente-Fernández, 2013). Yet, very little is known about factors contributing to the course and progression of these disease features.

Pesticide exposures have consistently been associated with the development of PD (Freire and Koifman, 2012), but to date no epidemiologic studies have investigated the influence of pesticides on PD symptom progression. Pesticide exposures can induce oxidative stress and mitochondrial dysfunction and impair the ubiquitin-proteasome system, mechanisms that have been related to neuronal cell death in PD (Rhodes et al., 2013; Terry, 2012). For these same reasons, it is possible

* Corresponding author at: UCLA, Epidemiology, Box 951772, Los Angeles, CA 90095, USA.
E-mail address: britz@ucla.edu (B. Ritz).

http://dx.doi.org/10.1016/j.envint.2017.06.018
Received 31 March 2017; Received in revised form 8 June 2017; Accepted 22 June 2017
Available online 06 July 2017

that these exposures may also contribute to faster symptom progression. Organophosphate (OP) insecticides are among the most commonly used pesticides agriculturally. The National Health and Nutrition Examination Survey (NHANES), 1999–2000, found that > 50% of participants in this national population sample had measurable levels of OP pesticide metabolites in their urine (NHANES, 2011). OPs have long been investigated in relation to PD susceptibility both due to neurotoxic action and their ability to induce oxidative stress among other mechanisms (Bagchi et al., 1995; Lukaszewicz-Hussain, 2010; Terry, 2012).

Additionally, OPs have been associated with other PD related non-motor symptoms. In general populations, OP pesticides have been reported as contributing to cognitive impairment, inducing deficits in signal detection, information processing, attention, and memory among others, and been linked to depression and suicide (Jaga and Dharmani, 2007; London et al., 2005; Terry, 2012; Zaganas et al., 2013). Animal studies have provided some support for these observations, finding that chronic, low level OP exposure (1) is associated with sensorimotor gating, spatial learning, recognition memory, cognitive flexibility and sustained attention (Terry, 2012), and (2) influences serotonin levels, possibly explaining how OP exposures may influence mood (Aldridge et al., 2005; London et al., 2005; Slotkin and Seidler, 2008).

Many OP pesticides are activated to a toxic analog (oxon) by cytochrome P450 (Costa et al., 2003), and the oxon is subsequently detoxified by the paraoxonase activity of the PON1 hydrolyzing enzyme (Costa and Furlong, 2007). Activity of PON1 is influenced by common single nucleotide polymorphisms (SNPs) in the *PON1* gene, including *PON1* L55M (rs854560). *PON1* L55M has been shown to directly influence PON1 levels and activity (Brophy et al., 2001; Garin et al., 1997; Mackness et al., 1993). We have previously reported statistical interactions between this variant and OP exposures related to PD risk (Lee et al., 2013), and there is evidence for a role of PON1 in Alzheimer's and vascular dementia, potentially through its anti-atherosclerotic function (Wehr et al., 2009; Zhub et al., 2015). PON1 is an arylesterase, responsible for metabolism of aromatic esters (Cervellati et al., 2014). Both paraoxonase and arylesterase activities of the protein are responsible for the anti-inflammatory and antioxidant activities of high density lipoprotein (HDL) and PON1 has been shown to prevent LDL oxidation in-vitro (Cervellati et al., 2014).

Here, we will investigate whether long-term low level estimated ambient agricultural OP exposure assessed with a geographic information system (GIS) that employed pesticide use reports and land use information, and *PON1* L55M genetic variation act together to influence the rate of motor, cognitive, and mood symptom progression in PD. We will rely on a prospectively followed population-based cohort of Parkinson's patients from three highly agricultural Central California counties, followed on average for more than seven years into their disease course.

2. Methods

All procedures described were approved by the University of California at Los Angeles (UCLA) Human Subjects Committee and informed consent was obtained from all participants.

2.1. Study population

This longitudinal cohort includes 246 PD patients recruited as part of the Parkinson's Environment and Gene (PEG) population-based case-control study in Central California. More detail on recruitment methods (Costello et al., 2009; Gatto et al., 2010) and case definition criteria (Kang et al., 2005) for the case-control study and the longitudinal cohort (Ritz et al., 2012) have been published previously. Briefly, 373 incident, idiopathic PD patients, diagnosed within 3 years of recruitment, compose the base population for this longitudinal cohort. All patients were seen by movement disorder specialists (JB, YB) at least once at baseline, many on multiple occasions, and confirmed as having probable idiopathic PD based on published criteria (Hughes et al., 1992). At the first follow-up after baseline (on average 3.5 years after baseline), 108 patients were lost to follow-up (64 were deceased, 6 too ill, 17 withdrew, and 21 could not be re-contacted). We successfully re-examined 265 patients during follow-up, and 13 of these participants were re-classified as not having idiopathic PD upon examination. Of the remaining 252 PD patients, 246 provided the data necessary for this investigation. Of these patients, 65 (26%) participated in 2 exams (3.6 years of mean follow-up, 5.9 years into disease), 174 (71%) in 3 exams (5.7 years of mean follow-up, 7.6 years into disease), and 7 (3%) participants in 4 exams (6.3 years of mean follow-up, 8.0 years into disease).

2.2. Assessment of PD progression

Trained interviewers collected detailed information on demographic and risk factors and for each participant UCLA movement disorder specialists conducted physical examinations at baseline and during each follow-up to assess progression. Specifically, motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part III, which assesses speech, facial expression, tremor, rigidity, hand, arm, and leg movements, posture, gait, postural stability, and bradykinesia. If possible, patients were examined off PD medications (82% of the baseline exams and 80% of follow-up exams). For patients who we could only examine on medication, we estimated an off-score by adding the difference of the whole study population's mean off- and mean on- scores at the time of exam to the patient's on-score (Ritz et al., 2012). Cognitive function was assessed at each exam with the Mini-Mental State Exam (MMSE), a widely used 30-point instrument that tests for orientation, attention, memory, language, and visual-spatial skills. For 3 patients at baseline and 6 during the first follow-up exam, we had to substitute the in-person MMSE with a 26-point telephone version of the MMSE and applied validated weights to make these scores comparable as recommended (Newkirk et al., 2004). Finally, we used the Short Form Geriatric Depression Scale (GDS) to measure depression symptoms with 15 questions it has been widely used and validated in older populations (Burke et al., 2015). We previously validated the GDS in our PD population, finding high sensitivity and positive predictive value compared with the Structured Clinical Interview for DSM Disorders (SCID) and Patient Health Questionnaire (PHQ-9) instruments (Thompson et al., 2011).

2.3. Organophosphate exposure assessment

We estimated ambient exposure to OP pesticides based on residential or occupational proximity to pesticide application, primarily from commercial agricultural applications. We used a geographic information system (GIS) based computer model which links California state mandated pesticide use reports (CA-PUR) for all commercial pesticide application since 1974, which contain information on date, location, type and amount of pesticide applied (provided within 1-sq. mile grids) (CDPR, 2013), with land use surveys, providing the location of specific crops and used to assess a more precise location of application within the 1-sq. mile CA-PUR grid (CDWR, 2013), and geocoded lifetime address histories for each of our participants (both residential and occupational addresses). For each pesticide reported to the CA-PUR, we calculated the pounds applied per year within a 500-m buffer of each residential and occupational address of our participants since 1974.

A total of 36 pesticides are considered OPs in the pesticide action network (PAN) pesticide database (Kegley et al., 2014) and contributed to our OP exposure measure; for a more detailed description see (Paul et al., 2015). Briefly, for each pesticide, we summed the pounds of pesticide applied per year and per acre within the 500-m buffer of each address within the study-period (1974-baseline interview), and then