Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease

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ABSTRACT

Objectives: Traumatic brain injury (TBI) increased risk of Parkinson disease (PD) in many but not all epidemiologic studies, giving rise to speculations about modifying factors. A recent animal study suggested that the combination of TBI with subthreshold paraquat exposure increases dopaminergic neurodegeneration. The objective of our study was to investigate PD risk due to both TBI and paraquat exposure in humans.

Methods: From 2001 to 2011, we enrolled 357 incident idiopathic PD cases and 754 population controls in central California. Study participants were asked to report all head injuries with loss of consciousness for >5 minutes. Paraquat exposure was assessed via a validated geographic information system (GIS) based on records of pesticide applications to agricultural crops in California since 1974. This GIS tool assesses ambient pesticide exposure within 500 m of residences and workplaces.

Results: In logistic regression analyses, we observed a 2-fold increase in risk of PD for subjects who reported a TBI (adjusted odds ratio [AOR] 2.00, 95% confidence interval [CI] 1.28–3.14) and a weaker association for paraquat exposures (AOR 1.36, 95% CI 1.02–1.81). However, the risk of developing PD was 3-fold higher (AOR 3.01, 95% CI 1.51–6.01) in study participants with a TBI and exposure to paraquat than those exposed to neither risk factor.

Conclusions: While TBI and paraquat exposure each increase the risk of PD moderately, exposure to both factors almost tripled PD risk. These environmental factors seem to act together to increase PD risk in a more than additive manner. *Neurology*® 2012;79:2061–2066

GLOSSARY

AOR = adjusted odds ratio; **CI** = confidence interval; **GIS** = geographic information system; **OR** = odds ratio; **PD** = Parkinson disease; **RERI** = relative excess risk due to interaction; **RR** = relative risk; **TBI** = traumatic brain injury.

Parkinson disease (PD), the second most common neurodegenerative disorder affecting 1%–2% of the population over 65 years of age, is characterized by progressive loss of dopamine neurons in substantia nigra pars compacta, leading to bradykinesia, rigidity, postural instability, and resting tremor as the cardinal motor features. It is widely acknowledged that PD etiology is most likely multifactorial. Lifestyle habits such as smoking and caffeine intake, genetic polymorphisms, environmental exposures to pesticides or metals, long-term exposure to certain medications, and interactions between these factors collectively appear to contribute to disease development. We have previously reported 2- to 3-fold increases in risk of developing PD when exposed to specific types or classes of pesticides, especially for combined exposures to paraquat and maneb, and for patients who carry genetic polymorphisms in susceptibility genes.^{1,2}

In the past 20 years, many but not all studies of traumatic brain injury (TBI) have linked head injuries with or without loss of consciousness to PD.^{3–10} We speculated that TBI may require additional risk or susceptibility factors in order to cause PD, which has sometimes been referred

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to as the “multiple hit” hypothesis of PD.¹¹ Recently, an animal study demonstrated that even though a single exposure to a mild TBI was sufficient to cause a progressive loss of nigrostriatal dopaminergic neurons, the number of dopaminergic neurons lost was much larger when TBI was accompanied by exposure to paraquat at a dose that by itself did not cause a significant loss of nigrostriatal dopaminergic neurons.¹² Specifically, an insult such as TBI may simply increase the vulnerability of dopaminergic neurons to additional insults, including toxic agents such as pesticides. Herein, utilizing our unique exposure data from a population-based case-control study with a well-characterized PD phenotype, we present evidence that exposure to both TBI and paraquat in humans increases risk for developing PD.

METHODS Subjects. This case-control study enrolled patients with incident idiopathic PD between January 1, 2001, and January 1, 2007, and population-based controls from 3 mostly rural agricultural counties (Kern, Tulare, Fresno) in central California between 2002 and 2011. Subject recruitment methods¹³ and case definition criteria¹⁴ have been described in detail elsewhere.

Cases with a PD diagnosis within 3 years of enrollment (2001–2007), not in the last stages of a terminal illness, residing in the tri-county study area at the time of recruitment, and residing in California for at least 5 years before recruitment were recruited through neurologists, large medical groups, and public service announcements. Of 1,167 patients with PD initially identified, 604 did not meet eligibility criteria: 397 had their initial PD diagnosis more than 3 years prior to recruitment, 134 lived outside the tri-county area at the time of recruitment, 51 had a diagnosis other than PD, and 22 were too ill to participate. Of the 563 eligible cases, 90 could not be examined (56 declined to participate or moved away, 18 had become too ill to be examined, and 16 died prior to the scheduled appointment). Of the 473 subjects examined by University of California at Los Angeles movement disorder specialists (J.B. and Y.B.), 94 did not meet published criteria for idiopathic PD^{15,16} when examined or re-examined during the initial study period, an additional 13 were reclassified as not idiopathic PD during our follow-up study,¹⁷ 6 subjects withdrew between examination and interview, and 3 cases were diagnosed after January 2007, our enrollment close-out date. Only the remaining 357 PD cases contributed to this analysis.

Eligibility criteria for controls included not having Parkinson disease, being at least 35 years of age, residing in the tri-county study area at the time of recruitment, and residing in California for at least 5 years prior to recruitment. Population-based controls were recruited initially from Medicare lists (2001) and, after the Health Insurance Portability and Accountability Act (HIPAA), from residential tax assessor records from the tri-county area. Two sampling strategies were implemented to increase enrollment success and achieve representativeness of the control population, including 1) random selection of residential parcels which we enrolled via mail and phone¹³; and 2) random selection of 5 households per cluster, each visited in person by study staff members up to 4 times to determine eligibility and to recruit subjects.

We defined clusters based on the random selection of 1 residential address in the tri-county area plus 4 other addresses in close proximity to the selected address.

Of the 1,212 potential controls contacted through the first sampling strategy, 457 were ineligible: 409 were <35 years of age, 44 were too ill to participate, and 4 primarily resided outside the study area. From among 755 eligible population controls, 409 declined, became too ill to participate, or moved out of the area after screening and prior to enrollment. Another 5 controls provided only partial information and were excluded. Of the 4,756 individuals screened for eligibility through the second sampling strategy, 3,515 were ineligible (88% due to age criteria). From 1,241 eligible population controls, 634 declined participation. There were 607 population controls enrolled under the second sampling strategy. We also excluded 183 controls who completed only an abbreviated questionnaire, 8 controls who lacked relevant exposure information, and 3 cognitively impaired controls. Thus, our study included 341 controls identified by mail or phone and 413 controls identified in-person (total $n = 754$) with all information necessary for inclusion in this analysis.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all subjects, and the study was approved by the UCLA Institutional Review Board.

Traumatic brain injury and ambient paraquat exposure. Cases and controls provided information on demographics, detailed lifetime residential, workplace address, and medical histories, and behavioral risk factors in interviews. As part of the medical history interview, participants reported ever having experienced a head injury with loss of consciousness for over 5 minutes, their age at the time of the event, and whether they had been hospitalized. We defined TBI as having reported a head injury with loss of consciousness for more than 5 minutes.

Ambient residential and workplace exposures to paraquat were estimated for each study participant using a validated geographic information system (GIS)-based system.¹⁸ This GIS system combined pesticide use report data collected by the California Department of Pesticide Regulation since 1974, land use maps created by the California Department of Water Resources, and geocoded address information for all reported residential and workplace addresses. The GIS-based system estimates ambient pesticide exposure around homes or workplaces resulting from pesticide applications to agricultural crops, and has been described in detail elsewhere.^{19,20} Briefly, for each participant's residential and workplace address from 1974 to 1999, we estimated pounds of paraquat applied per acre for a 500-m buffer around the home or workplace, weighting the total poundage by the proportion of the acreage treated. We then calculated an average study period exposure estimate by summing the year-specific values and dividing by the total study period (26 years, from 1974 to 1999). We considered participants exposed to paraquat if they had an average study period exposure greater than 0 at both their residential and their workplace addresses. We calculated paraquat exposure up to 1999 in order to restrict our exposure of interest to the time before most of our patients with PD were diagnosed; i.e., our patients were first diagnosed between 1999 and 2007.

Statistical analysis. Demographic characteristics were compared between cases and controls using the Student t test for continuous variables and the Pearson χ^2 test for categorical variables. To assess the main effects of both TBI and paraquat on PD, we employed unconditional logistic regression analyses to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Table 1 Demographic characteristics of the study population by PD status

	Cases (n = 357)	Controls (n = 754)	p Value ^a
Gender, n (%)			
Female	152 (42.6)	402 (53.3)	<0.001
Male	205 (57.4)	352 (46.7)	
Age, y, ^b mean (SD)	68.3 (10.2)	66.9 (11.2)	0.04
Race,^c n (%)			
Caucasian	287 (80.4)	526 (70.0)	<0.001
Non-Caucasian	70 (19.6)	226 (30.0)	
Education, y, mean (SD)	13.4 (4.1)	13.9 (4.0)	0.06
County, n (%)			
Fresno	163 (45.7)	310 (41.1)	0.06
Kern	126 (35.3)	322 (42.7)	
Tulare	68 (19.0)	122 (16.2)	
Cigarette smoking, n (%)			
Never	187 (52.4)	364 (48.3)	0.20
Ever	170 (47.6)	390 (51.7)	
First-degree relative with PD,^d n (%)			
Yes	52 (14.6)	63 (8.7)	0.002
No	305 (85.4)	664 (91.3)	

Abbreviation: PD = Parkinson disease.

^a Student t test for continuous variable and Pearson χ^2 test for categorical variables.

^b Age at diagnosis for patients with PD and age at interview for controls.

^c Missing: race (n = 2).

^d Twenty-seven controls did not report family history; we assumed that their first-degree relative did not have PD.

We examined multiplicative interactions between TBI and paraquat by introducing a product term into logistic regression models. It has been suggested that biological and public health interactions should be assessed on an additive rather than a multiplicative scale; a positive departure from additivity of the estimated effects means that the combined effect of 2 exposures is larger than the sum of each individual effect.²¹ Thus, we also examined interactions on the additive scale by calculating the relative excess risk due to interaction (RERI), which is defined as $RR_{11} - RR_{10} - RR_{01} + 1$, where RR_{ij} denotes the relative risk and i and j are used to denote the presence (=1) or absence (=0) of 2 separate exposures. We used the delta method proposed

by Hosmer and Lemeshow²² to calculate the 95% CI for RERI. Since the incidence of PD is rare, we used ORs to estimate relative risks (RR). In all regression models, we adjusted for age (continuous, defined as age at PD diagnosis for cases and age at enrollment for controls), gender (male, female), smoking status (ever, never), race (Caucasian, non-Caucasian), county (Fresno, Tulare, Kern), and education (continuous, in years). For main effects, we conducted sensitivity analyses stratifying by gender. For interaction analyses, we performed additional sensitivity analyses excluding 1) participants who reported head trauma that had occurred within 10 years of index date (PD diagnosis for cases or interview date for controls); 2) those not hospitalized at the time of the head injury; and 3) population controls recruited from the same cluster who had lived at the recruitment address for more than 2 years prior to 1999 (i.e., we excluded 23 controls from 21 residential clusters by randomly sampling and including only 1 control from each such cluster). Subjects with missing head trauma information (n = 23) were excluded from main and interaction analyses.

RESULTS Participants with idiopathic PD were more likely to be male than population controls (table 1). Patients with PD were also slightly older and less likely to report ever having smoked cigarettes. The reported frequency of head trauma with over 5 minutes of unconsciousness was higher among cases than controls (table 2). We estimated a 2-fold increase in risk for developing PD for those experiencing TBI, and the effect estimate was slightly stronger for women than men (women, adjusted OR [AOR] = 2.61, 95% CI = 1.32–5.16; men, AOR = 1.71, 95% CI = 0.94–3.11). Up to 41% of our study population (n = 460) had ever been exposed to paraquat both at home and at workplaces (table 2). There was a moderate association with PD for those exposed residentially and occupationally, but no difference between men and women (results not shown).

When examining combined effects of ambient paraquat exposures and TBI, we observed a 3-fold risk increase for subjects who reported a TBI and had also been exposed to paraquat at both home and workplaces, compared with persons who had never experienced TBI or been exposed to paraquat (table 3). Compared to those without either TBI or paraquat exposure, we observed 31%–78% increases in risk for those exposed

Table 2 Associations between traumatic brain injury, ambient paraquat exposure, and Parkinson disease

	Cases n = 357, n (%)	Controls n = 754, n (%)	Crude model	Adjusted model ^a
Head trauma^b				
No	315 (88.2)	681 (93.2)	1.0	1.0
Yes	42 (11.8)	50 (6.8)	1.82 (1.18–2.80)	2.00 (1.28–3.14)
Ambient residential and workplace exposures				
No	188 (52.7)	463 (61.4)	1.0	1.0
Yes	169 (47.3)	291 (38.6)	1.43 (1.11–1.84)	1.36 (1.02–1.81)

^a Adjusted for age (continuous), gender, ever smoked, race, county, education (school years).

^b Missing head trauma information for 23 subjects.

Table 3 Effect estimates (ORs and 95% CI) for interactions between ambient residential and workplace exposures to paraquat, traumatic brain injury, and Parkinson disease

	Never exposed			Ever exposed		
	No. cases/controls	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	No. cases/controls	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
Head trauma						
No	167/419	1.0	1.0	148/262	1.42 (1.08-1.86)	1.31 (0.97-1.77)
Yes	21/31	1.70 (0.95-3.04)	1.78 (0.98-3.26)	21/19	2.77 (1.45-5.29)	3.01 (1.51-6.01)
OR (95%) for interaction					1.15 (0.48-2.76)	1.29 (0.52-3.19)

Abbreviations: CI = confidence interval; OR = odds ratio.

^aAdjusted for age (continuous), gender, ever smoked, race, county, and education (school years).

to paraquat but who had not experienced TBI, and those who had experienced TBI but had not been exposed to paraquat. When examining interactions on an additive scale, we observed a higher than additive risk for those with combined exposure to paraquat and TBI (RERI = 0.92, 95% CI = -1.33 to 3.16; figure). All estimated effect sizes were very similar when we restricted our population to head traumas that had occurred 10 years prior to the index date (data not shown). Similarly, effect estimates for interactions did not change notably when we excluded participants who had not been hospitalized for head injuries or controls from clusters in which more than 1 resident had been living in their home for more than 2 years prior to 1999 (data not shown).

DISCUSSION Our study suggests a combined effect of 2 environmental exposures, TBI and paraquat exposure, on PD development that is larger than each component effect. These results in humans are supported by findings from a recent animal study in which the combination of experimental head trauma and subthreshold paraquat doses led to increased nigrostriatal dopaminergic neuron loss, and greater induction of α -synuclein accumulation and inflammation compared with experimental head trauma treatment alone.¹²

Our results for TBI and PD are consistent with findings from previous studies that reported head injuries as being associated with PD.^{3,6,7,9,10} A twin study reported a 4-fold increased risk for developing PD among subjects self-reporting a prior head injury (OR = 3.8, 95% CI = 1.3-11). Two case-control studies assessed head injuries based on medical record review rather than participant recall.^{3,8} One of these was a small study (196 patients with PD) that found associations for subjects with severe head injury requiring hospitalization, but included only 9 head trauma hospitalizations.³ The other very large medical record linkage study conducted in Denmark reported a 50% increase in risk of developing PD after hospital treatment for head injuries within 10 years prior to a PD diagnosis.⁸ This is consistent with our estimate for subject reports of head injuries requiring hospitalization (AOR = 1.77, 95% CI = 0.99-3.17).

Our new results for ambient paraquat exposure confirm our previous findings, but with a larger control group, and including exposures both at residences and workplaces.²³ A previous study in Taiwan reported occupational paraquat exposure to increase PD risk (OR = 3.2, 95% CI = 2.41-4.31).²⁴ More recently, a cohort study in the United States also reported ever being exposed to paraquat as being associated with PD (OR = 2.5, 95% CI = 1.4-4.7).²⁵ Although the effect estimates for PD and paraquat from these 2 studies are greater than ours (AOR = 1.36, 95% CI = 1.02-1.81), these results cannot easily be compared to our findings, due to differences in the types of exposure, i.e., occupational vs ambient paraquat exposures.

Similar to most previous studies, we collected TBI information through interviews, which might introduce bias due to differential recall by cases compared with controls. However, a previous head trauma and PD study⁶ observed perfect agreement between self-reports and medical record retrieval of information regarding head injuries in a subset of their sample. These authors also suggested that differential recall for head injuries is most likely for events that

Figure Relative risks (estimated from odds ratios) contributions from traumatic brain injury (TBI), paraquat, and combined TBI and paraquat exposures

occur closer in time to PD onset. When we excluded TBI reports close to PD onset, we observed similar size associations, suggesting no differences in recall depending on PD diagnosis. A major strength of our study is the availability of our GIS-based modeling system for long-term ambient residential and workplace paraquat exposures, using California pesticide use records. This exposure assessment tool avoids differential recall bias for historical exposure; however, nondifferential misclassification of exposure cannot be ruled out (e.g., due to geocoding errors and uncertainties concerning pesticide drift).

There are a number of biological mechanisms that may explain the associations we observed. TBI is known to induce an inflammatory cascade and accumulation of α -synuclein and tau, 2 proteins that are major components of Lewy bodies.^{26–31} Furthermore, TBI may contribute to PD through disruption of the blood–brain barrier and mitochondrial function.^{32–35} Most recently, a pooled epidemiologic study³⁶ observed an association (OR = 3.5, 95% CI = 1.4–9.2) between head injury and PD, but only among carriers of the α -synuclein (SNCA) Rep1 promoter risk allele, which has been previously associated with an increased risk of PD.^{36–38} In experimental animal studies, paraquat exposure can induce reactive oxygen species production in the brain, which may lead to loss of nigral dopaminergic neurons.^{39,40} This, combined with recent experimental animal data,¹² suggests that the physiologic process triggered by a head injury may increase the vulnerability of neurons to insults from neurotoxic pesticides, with the combination increasing the risk of PD more than each exposure on its own.

A recent animal study that examined the combined effects of TBI (first exposure) and low-dose paraquat exposure (subsequent exposure) in rats observed a synergistic effect of both exposures on nigrostriatal dopaminergic neuron loss with exposure to paraquat 3 and 6 days after TBI; however, this synergistic effect was not observed when paraquat was administered 21 and 22 weeks after TBI.¹² In the present study, we were unable to address temporality of TBI and paraquat exposures, since pesticide records were only available after 1974. Many of our study participants reported TBIs that had occurred at a young age (mean = 27 years; range = 2–82), i.e., during a period when pesticide exposures were not yet recorded in the California system. Another limitation of our study is that we were unable to examine the effect measure modification by gender since the relatively small number of cases exposed to both agents did not provide sufficient statistical power for gender stratification. Furthermore, our population-based case-control study was conducted in California's rural Central Valley, an area with substantial agricultural pesticide use. The high prevalence of pesticide exposure in this population

provided sufficient statistical power to examine interactions between paraquat exposure and TBI on PD risk. However, study results may not be generalizable to populations with low pesticide exposure.

While both TBI and paraquat exposures weakly or moderately increased PD risk, the magnitude of the combined effect estimate was stronger than the sum of the TBI and PD effects alone, indicating a positive interaction on an additive scale. Our data suggest that multiple environmental factors may act together to increase the risk of PD beyond the effect of each risk factor alone, and that some individuals might be developing PD due to an accumulation of multiple exposures.

AUTHOR CONTRIBUTIONS

Dr. Lee: analysis and interpretation of the data and writing of the manuscript. Dr. Bordon: acquisition of data including physical examination of patients, contributed to manuscript writing. Dr. Bronstein: acquisition of data including physical examinations of patients, contributed to manuscript writing. Dr. Ritz: study design and acquisition of data, contributed to analysis and interpretation of the data, revisions of the manuscript, study supervision, and obtained funding.

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DISCLOSURE

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