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Environmental risk factors and Parkinson's disease:

A case-control study in Taiwan

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Article abstract—To explore environmental risk factors for Parkinson's disease (PD) in Taiwan, we investigated 120 patients with PD and 240 hospital control subjects matched with patients on age (±2 years) and sex. Based on a structured open-ended questionnaire, we carried out standardized interviews to obtain history of exposure to environmental factors, including place of residence, source of drinking water, and environmental and occupational exposures to various agricultural chemicals. In the univariate analysis, the history of living in a rural environment, farming, use of herbicides/pesticides, and use of paraquat were associated with an increased PD risk in a dose-response relationship. After adjustment for multiple risk factors through conditional logistic regression, the biological gradient between PD and previous uses of herbicides/pesticides and paraquat remained significant. The PD risk was greater among subjects who had used paraquat and other herbicides/pesticides than those who had used herbicides/pesticides other than paraquat. There were no significant differences in occupational exposures to chemicals, heavy metals, and minerals between PD patients and matched control subjects. The duration of drinking well water and alcohol consumption was not significantly associated with PD. There was an inverse relationship between cigarette smoking and PD. Environmental factors, especially exposures to paraquat and herbicides/pesticides, may play important roles in the development of PD in Taiwan.

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The cause of Parkinson's disease (PD) is unknown. Epidemiologic surveys of PD conducted in various parts of the world suggest that the disease occurs worldwide.[1] The prevalence of PD varies widely in different countries, ranging from 14 per 100,000 in People's Republic of China[2] to 328 per 100,000 in the Parsi community in Bombay, India.[3] The prevalence of PD in Chinese population seems much lower than that in whites.[2,4] However, Wang et al.[5] reported that the prevalence of PD was 119 per 100,000 in Kin-

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men, Taiwan; this is much higher than in mainland China and similar to Western countries. This difference in PD prevalence between Taiwan and mainland China may be from potential genetic factors, environmental factors, or both.

Although the etiology of PD is still unknown, increasing evidence supports the hypothesis that environmental factors may contribute to its occurrence. Many epidemiologic studies have shown that living in a rural environment, farming, drinking well water, and occupational herbicide/pesticide exposure were related significantly to PD.[6-19] A neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), can cause the clinical, biochemical, and pathologic features of PD, suggesting similar neurotoxins may elicit PD.[20] MPTP is converted by the action of monoamine oxidase B to MPP^+ (1-methyl-4-phenylpyridinium ion), the effective toxin.[20] MPP^+ is used as an herbicide under the name Cyperquat and is chemically similar to some other commonly used herbicides, such as paraquat. Paraquat is widely used as a nonselective contact herbicide. Any link between such chemicals and PD would therefore have important public health implications.

Taiwan is a small island located to the southeast of mainland China. Cultivable land is limited in Taiwan because of dense population. To use cultivable land efficiently, herbicides/pesticides are extensively used in Taiwan. However, the association between PD and exposures to herbicides/pesticides and other risk factors in Taiwan has never been reported. To identify risk factors for PD in Taiwan, we carried out this case-control study.

Methods. One hundred twenty patients with PD and 240 hospital control subjects matched with patients on age (±2 years) and sex were studied. All PD patients were recruited from the Movement Disorder Clinic of National Taiwan University Hospital (NTUH) in Taipei between July 1993 and June 1995. At the same time, control subjects were recruited from the neurologic or medical outpatient clinics at the same hospital. There are nine medical centers on the whole Taiwan island. All could diagnose and treat PD. NTUH is a 2,000-bed teaching hospital and one of the major tertiary referral centers in Taiwan. Thus, the Movement Disorder Clinic and the neurologic and medical outpatient clinics serve essentially the same geographic population. Comparing the current rural residencies of patients and control subjects, the ratio is about 1:2.5. It fits the 1:2 case-matched control subjects. To examine environmental risk factors in Taiwan, PD patients and matched control subjects were restricted to those who were born and resided in Taiwan; immigrants from other countries or mainland China were excluded.

The diagnosis of PD was based on two or more cardinal signs of PD, including resting tremor, cogwheel rigidity, bradykinesia, and postural reflex instability, and responsiveness to levodopa therapy. Both PD patients and control subjects were examined by neurologists (H.H.L., J.S.J., Y.C.C., R.C.C.). Patients with atypical features suggesting a multiple system atrophy or secondary causes of parkinsonism, including drug, infection, tumor, previous cerebrovascular accident, or known toxins, were excluded. Control subjects were recruited from outpatient clinic patients with the following diagnoses: headaches, back pain, cervical spondylosis, and peripheral neuropathy. Individuals with exposure to neuroleptics and previous brain diseases such as stroke, infection, and dementia were not included in this study.

Information was collected according to a structured open-ended questionnaire by trained interviewers in a face-to-face interview with subjects and their family members, if available. Data included the years of residing in rural and urban areas, years of farming, drinking water sources and duration of consumption, and residential and occupational exposures to herbicides/pesticides, chemicals, heavy metals, and minerals. Subjects were asked to identify specific herbicides/pesticides, chemicals, heavy metals, and minerals they had used. The habits of cigarette smoking and alcohol drinking were also recorded. Because there were no previous studies on risk factors of PD in Taiwan, neither interviewers nor PD patients were aware of the study hypothesis. Twenty PD patients and 20 control subjects were reinterviewed as a check for reliability 4 to 10 months after initial interview. Results of all 40 reinterviews were identical to those of their corresponding initial interviews.

Age at the onset of PD was defined as the age at which the first symptom of PD became evident by patient's recollection. A positive exposure was defined as an occupational or residential contact with a given factor for at least 1 year before the onset of PD. For a given control, risk factor exposure was defined as occurring before the time of disease onset in the index case. Chi-square and odds ratios were calculated using the extended Mantel-Haenszel methods for two matched control subjects.[21] In the multivariate analysis of environmental risk factors for PD, conditional logistic regression models were used to estimate multivariate-adjusted odds ratios for the duration of living in rural areas, farming, and use of herbicides/pesticides and paraquat. Because the use of herbicides/pesticides and paraquat were highly correlated, only one of them was included in the multiple conditional logistic regression models to avoid the problem of hypercollinearity. Moreover, multivariate analysis for the combination of use of herbicides/pesticides and paraquat was performed.

Results. A total of 55 women and 65 men with PD were studied. Their mean age was 63.1 years with a range of 37 to 91 years. Mean age at PD onset was 58.3 years with a range of 28 to 85 years. Mean Hoehn and Yahr stage of PD patients was 2.3 with a range of 1 to 5. There were 110 women and 130 men in the control group. The mean age of the control subjects was 63.5 years with a range of 37 to 91 years.

Table 1 shows the dichotomous variable analysis to examine the association of PD in Taiwan. An increased risk of PD was observed for those who had ever lived in a rural area, showing an odds ratio (OR) of 2.04 (95% CI, 1.23 to 3.38), and for those who had ever engaged in farming (OR, 1.81; 95% CI, 1.25 to 2.64). An increased PD risk was found among farmers engaged in rice growing (OR, 1.7; 95% CI, 1.13 to 2.58) but not in orchards. There were significant associations between risk of PD and occupational or residential exposure to herbicides/pesticides (OR, 2.89; 95% CI, 2.28 to 3.66). Among the herbicides and

Table 1 Exposures to environmental factors of matched case-control sets and associated OR of developing PD in Taiwan

	Matched case-control sets*							
Exposure variable	+++	++−/+−+	+−−	−++	−+−/−−+	−−−	OR	95% CI
Living in rural residence	59	33	10	10	6	2	2.04	1.23–3.38†
Farming	13	36	21	10	23	17	1.81	1.25–2.64†
Growing rice	10	27	24	9	26	24	1.70	1.13–2.58†
Growing fruit	0	3	14	2	15	86	1.63	0.50–5.33
Herbicides/pesticides use	1	12	33	2	23	49	2.89	2.28–3.66‡
Paraquat use	1	2	28	1	16	72	3.22	2.41–4.31‡
Chemicals exposure	0	2	6	1	5	106	2.00	0.16–24.7
Heavy metals exposure	0	1	5	1	5	108	1.57	0.002–1416
Minerals exposure	0	1	3	0	1	115	7.00	0.16–302
Drinking well water	49	34	7	17	11	2	1.07	0.19–5.98
Drinking spring water	0	2	12	0	19	87	1.55	0.90–2.67
Drinking pond water	0	3	7	0	23	87	0.74	0.02–35
Cigarette smoking	16	11	4	15	15	59	0.42	0.25–0.70‡
Drinking alcohol	8	10	7	11	19	65	0.59	0.26–1.33

* Exposure status of patient and two matched control subjects, e.g., ++− indicating patient and one control subject were positive.
† $p < 0.05$.
‡ $p < 0.01$ based on chi-square test.

pesticides, there was a strong association between paraquat exposure and PD risk (OR, 3.22; 95% CI, 2.41 to 4.31).

Occupational exposures to chemical, heavy metals, and minerals were not significantly associated with the risk of PD. The source of daily water intake such as well water, spring water, or pond water had no relation to the development of PD. No association with PD was observed for drinking alcohol either. There was an inverse relationship between cigarette smoking and PD in Taiwan (OR, 0.42; 95% CI, 0.25 to 0.70).

Table 2 shows the trichotomous variable analyses, both univariately and multivariately, to examine the dose-response relationship between exposures to environmental factors and PD without and with adjustment for other environmental factors. In univariate analyses, there were significant associations between PD risk and the duration of cumulative lifetime exposure to rural residence, farming, herbicides/pesticides, and paraquat use. To estimate multivariate-adjusted ORs for environmental factors, two conditional logistic regression models were used to assess associations with PD risk for use of herbicides/pesticides (model I) and use of paraquat (model II) separately. As shown in table 2, the associations with PD risk for previous use of herbicides/pesticides (model I) and paraquat (model II) remained statistically significant after adjustment for other environmental factors. No significant increase in PD risk was observed for the history of living in rural residence, farming, and drinking well water after adjustment for the use of herbicides/pesticides or paraquat. The inverse relationship between cigarette smoking and risk of PD remained significant in the multiple conditional logistic regression analyses.

Compared with those who had no exposure to herbicides/pesticides as the referent, those who had used herbicides/pesticides other than paraquat had an OR of 2.17 (95% CI, 0.85 to 5.57), and those who had used paraquat with/without other herbicides/pesticides had an OR of 4.74 (95% CI, 1.95 to 11.52). Among subjects who were exposed to herbicides/pesticides, 67% of PD cases (28/42) and 50% of control subjects (18/36) had ever been exposed to paraquat. The OR of developing PD was 2.0 ($p < 0.01$) among those who had used paraquat and other herbicides/pesticides compared with those who had been exposed to herbicides/pesticides other than paraquat.

Discussion. The results of the univariate conditional logistic regression analysis suggest that individuals having any of the following risk factors are at an increased PD risk: living in a rural environment for more than 20 years, farming (especially in rice growing) for more than 20 years, or using herbicides/pesticides or paraquat. The univariate data also suggest a dose-response relation between the duration of cumulative lifetime exposure to these environmental factors and the PD risk. However, in the multiple conditional logistic regression analysis, only the occupational use of herbicides/pesticides and paraquat remained significant risk factors for PD in Taiwan. Having a history of occupational herbicides/pesticides and paraquat use was associated with a significant increase in PD risk of about four- to sevenfold after other environmental factors were adjusted.

After adjustment for previous occupational herbicides/pesticides and paraquat use, the increased PD risk associated with rural residence and farming were no longer significant, thus indicating that the risk associated with these exposures observed in the univariate analysis was likely due to the associations of herbicides/pesticides and paraquat exposure with rural residence and farming. Although rural living and farming might serve as a risk factor for identify-

Table 2 Univariate and multivariate analysis for the association between PD and environmental factors in Taiwan

			Univariate		Multivariate-adjusted OR			
					Model I		Model II	
Exposure variable	Patient no.	Control subject no.	OR	95% CI	OR	95% CI	OR	95% CI
Duration of living in rural residence (yr)								
0	18	63	1.00		1.00		1.00	
1–19	12	44	1.23	0.55–2.78	1.29	0.53–3.16	1.23	0.51–2.98
≥20	90	133	2.10	1.16–3.82*	1.73	0.84–3.59	1.68	0.81–3.47
Duration of farming (yr)								
0	50	135	1.00		1.00		1.00	
1–19	22	39	1.80	0.95–3.41	1.30	0.61–2.78	1.54	0.73–3.23
≥20	48	66	1.77	1.07–2.43*	0.54	0.23–1.22	0.85	0.43–1.69
Duration of using herbicides/pesticides (yr)								
0	74	199	1.00		1.00		—	—
1–19	14	21	1.48	0.64–3.43	1.41	0.52–3.85	—	—
≥20	32	20	4.50	2.33–8.69†	6.72	2.62–17.21†	—	—
Duration of using paraquat (yr)								
0	89	218	1.00		—	—	1.00	
1–19	7	13	1.19	0.35–4.03	—	—	0.96	0.24–3.83
≥20	24	9	6.41	2.74–15.00†	—	—	6.44	2.41–17.2†
Duration of consuming well water (yr)								
0	30	63	1.00		1.00		1.00	
1–19	15	51	0.67	0.33–1.36	0.59	0.26–1.34	0.58	0.26–1.32
≥20	75	126	0.98	0.59–1.64	0.75	0.42–1.35	0.71	0.40–1.28
Duration of smoking cigarettes (yr)								
0	89	152	1.00		1.00		1.00	
1–19	10	9	0.38	0.13–1.11	0.38	0.12–1.22	0.44	0.13–1.45
≥20	21	79	0.42	0.21–0.83†	0.43	0.21–0.90*	0.43	0.20–0.90*

Model I: Duration of living in rural residence, duration of farming, duration of using herbicides/pesticides, duration of consuming well water, and duration of smoking cigarettes were included in the regression model. Model II: Duration of living in rural residence, duration of farming, duration of using paraquat, duration of consuming well water, and duration of smoking cigarettes were included in the regression model.

* $p < 0.05$.
† $p < 0.01$ based on tests for statistical significance of regression coefficients.

ing potentially high-risk groups that may have direct contact with herbicides/pesticides and paraquat, they should still be regarded as risk factors for PD in Taiwan.

Because the questions asked in the interviews were straightforward on both residential and occupational histories, it is quite unlikely to result in differential recall bias, although some nondifferential recall loss may result in an underestimation of OR for risk factors. In this study, we asked only total duration in years for exposure to environmental factors; we cannot further analyze the OR for exposures at various intervals before PD onset.

Previous epidemiologic studies have suggested possible role of pesticides and herbicides as causative environmental agents for PD. Hertzman et al.[18] found a significant association between PD and an occupation of handling or directly contacting pesticides in British Columbia. Semchuk et al.[22] conducted a population-based case-control study in Calgary; previous occupational herbicide use was the only significant predictor of PD risk after multivariate adjustment. However, they also found that a family history of PD and a history of head trauma exceed herbicide exposure in importance as independent risks.[23] We did not assess the family PD history and head trauma in this study. Seidler et al.[19] reported a significant association between PD and pesticide use but not between PD and other rural factors in Germany. Reports from Hong Kong also have similar close relationship between herbicides/pesticides and PD. Ho et al.[13] found subjects who had previously used herbicides/pesticides had a 3.6-fold increased risk of developing PD in Hong Kong. Our results concurred with previous observations. Exposure to herbicide/pesticide for 20 or more years had a PD risk of 6.7-fold in Taiwan.

Several investigators suggest paraquat is a causal factor for PD.[7,24,25] Bocchetta and Corsini[26] reported two patients believed to suffer from paraquat-induced parkinsonism. Sanchez-Ramos et al.[27] reported a farmer who had been exposed to paraquat and affected with PD. Sechi et al.[28] reported a farmer in Italy who developed a severe parkinsonian syndrome several days after having sustained about a 10-minute exposure of the hands to a 10% aqueous solution of the contact herbicide diquat dibromide. Barbeau et al.[7] identified an increased prevalence of PD in areas of Quebec where farming was common. They postulated the widely used herbicide, paraquat, may cause PD.[7,24] However, Koller[29] did not find any evidence that paraquat was related to PD. Paraquat is a widely used herbicide in Taiwan. Farmers use it extensively in the rice field. In this study, subjects who previously used both paraquat and other herbicides/pesticides had a 4.74-fold increased risk of developing PD compared with subjects who used herbicides/pesticides other than paraquat and had a 2.17-fold increased risk of developing PD. The OR of developing PD was 2.0 among those who had used paraquat and other herbicides/pesticides compared with those who had been exposed to herbicides/pesticides other than paraquat. Paraquat might play an important role in the pathogenesis of PD.

The exposure to well water was not associated with the development of PD in Taiwan. The tap water supply system in Taiwan was not well established until the late 1970s. The results of our study indicate that the consumption of well water was common not only among PD patients but also among matched control subjects. The same observation that a past history of using well water as the source of drinking water was not associated with the risk of PD has been reported.[12,14,30] Koller et al.[15] found that drinking well water in childhood was associated with an increased risk of PD in the environmental analysis; however, it was found to be dependent on rural living in multivariate analyses. Although several studies have found drinking well water to be associated with an increased risk of PD,[9,11,16] Rajput and Uitti[31] attempted to identify a single responsible agent, without success.

Our results showed a decreased risk of developing PD among subjects who smoked cigarettes. Several case-control studies[18,32-35] have indicated that patients with PD were less likely to smoke cigarettes than health control subjects. This leads to the inference that smoking may protect against this disorder. In animal experiments, the substance contained in cigarettes may reduce the risk of developing PD by protecting the substantia nigra from potentially toxic effects of oxidative radicals produced in the metabolism on dopamine.[36-38] However, cessation of smoking may be related to a change in personality or a so-called "premorbid attitude" that may exist in patients who develop PD.[17,24,39,40]

Including our study, there are three studies on the risk factors for PD in the Chinese.[12,13] Compared with mainland China, Taiwan and Hong Kong are generally regarded as having a more advanced level of economic development and prosperity. The PD prevalence in China[2,4] was much lower than that in Taiwan[5] and Hong Kong.[13] The risk factors for PD in China were not the same as those in Taiwan and Hong Kong. In China, occupational or residential exposures to some industrial chemicals were associated with the development of PD, whereas living in rural villages had an inverse association with PD.[12] However, in Hong Kong, subjects who had lived in rural areas for a long duration, had been engaged in farming, had a history of previous use of herbicides and pesticides, and had habitually consumed raw vegetables were found to have an increased risk of PD. In Taiwan and Hong Kong, the prevalence and risk factors for PD are similar to those in Western countries.[13] These studies in Chinese populations disclose that environment and agriculture and industrial developments may play important roles in the pathogenesis of PD. The association between PD and environmental factors has consistently been observed among various racial groups in areas with high and low incidence of PD.[1] Our findings supported the possibility that environmental factors may be more important than racial factors in the pathogenesis of PD.

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