

Association Between Parkinsonism and Participation in Agriculture in Korea

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Background and Purpose: Environmental factors might influence the pathogenesis of Parkinson's disease (PD) or multiple-system atrophy (MSA), and previous examinations of pesticide exposure, well-water drinking, and farming have produced inconclusive results. Because agriculture has been of considerable importance to Korean society, and hence the risk of exposure to pesticides was high in Korea, this study investigated whether such exposure is associated with elevated risks of developing PD and MSA.

Methods: Two hundred and thirty-five PD patients, 133 MSA patients, and 77 normal control subjects were examined. Data concerning environmental factors were collected by face-to-face interviews using a structured questionnaire. Odds ratios (ORs) were calculated by binary logistic regression.

Results: ORs for environmental risk factors for developing PD were 1.06 [95% confidence interval (CI) = 1.02–1.10] for age and 2.37 (95% CI = 1.32–4.27) for rural well-water drinking for >10 years. Smoking >10 pack-years (OR = 0.31; 95% CI = 0.11–0.64) was a preventable factor for developing PD in this study. However, no significant risk factors were identified for MSA.

Conclusions: These results suggest that exposure to certain environmental risk factors plays a role in the development of PD. However, the development of MSA appears to be independent of environmental risk factors in Korean patients.

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Key Words: Parkinson's disease, Multiple-system atrophy, Pesticide, Well water, Smoking

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is characterized by preferential degenerative changes of dopaminergic neurons in the substantia nigra pars compacta and the appearance of

Lewy bodies. In most cases the specific cause of PD is not known, but there have been suggestions that both genetic and environmental factors are involved. However, familial parkinsonism is rare,¹ and genetics appears to play only a minor role in sporadic PD. The discovery that parkinsonism is induced by the neurotoxin MPTP² prompted searches for other PD-

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inducing environmental risk factors. Epidemiologic studies indicate that several environmental factors increase the risk of PD development, including exposure to well water,³⁻⁹ rural residency,^{3-5,8,10} farming,^{7,8,10,11} and contact with pesticides.^{8,10-14}

Multiple-system atrophy (MSA) is a neurodegenerative disease that is characterized by parkinsonism, cerebellar dysfunction, and autonomic insufficiency. Although the etiology of MSA has not been elucidated, several studies have suggested that exposure to pesticides is associated with MSA.¹⁵⁻¹⁷ Individuals can be exposed to pesticides either directly, such as by applying pesticides in agricultural, occupational, or residential settings, or indirectly, such as by drinking well water contaminated by pesticides. The associated epidemiological studies have varied considerably in terms of their regional and societal settings and the likely levels of exposure. Moreover, levels of environmental contamination by pesticides are likely to differ markedly by region and even more so between countries, because levels of human exposure in occupational or residential settings are influenced by both application methods and individual behaviors.

Korea was originally an agricultural society, but rapid industrialization over the past 50 years has led to only 5~6% of the Korean population nowadays participating in farming. Nevertheless, many elderly men and women are likely to have been exposed to pesticides over prolonged periods of time. This study was undertaken to investigate the associations of pesticide exposure with PD and MSA in the Korean population.

MATERIALS AND METHODS

1. Subjects

The participants were recruited from Seoul National University Hospital, and comprised 235 PD patients, 133 MSA patients, and 77 normal health-screening controls. Only patients aged over 50 years were recruited because genetic factors are believed to play an important role in early-onset PD. PD was diagnosed

according to the criteria of the United Kingdom Parkinson's Disease Society brain bank, although the criterion of a positive family history was not applied.¹⁸ All MSA subjects were diagnosed as having probable MSA according to the Consensus Criteria.¹⁹

2. Procedures

Information was collected by trained interviewers during face-to-face interviews using a structured questionnaire. The questionnaire included detailed information on duration of participation in farming, farming type, tap-water and well-water drinking, number and severity of pesticide intoxications, number and severity of carbon monoxide (CO) intoxications, and smoking history. Data related to pesticides included the annual frequency of pesticide spraying and the duration of farming. The pesticides poisoning data included the number and severities of acute poisoning episodes. Mild, moderate, and severe poisoning was defined as the presence of symptoms such as headache, nausea, vomiting, dizziness, abdominal pain, diarrhea, and general malaise; visual disturbance, dysarthria, muscular spasm, bradycardia, and gait disturbance; and mental change, generalized seizure, respiratory difficulty, and hospitalization; respectively. Smoking was recorded in units of pack-years, defined as the number of packs per day times the number of smoking years. Enrolled subjects were classified as drinkers or nondrinkers, where drinkers were further classified into three groups based on the number of 360 ml bottles of 'soju' (containing 20% alcohol) consumed per day: <1 bottle, 1 or 2 bottles, and 3~5 bottles.

3. Statistical methods

SPSS for Windows (release 13.0) was used for all analyses. The chi-square test was used to compare categorical variables, and risk variables were used to calculate odds ratios (ORs). The categorical variables of well-water drinking history (both rural and urban), rural well-water drinking history, farming for longer than 5 years, positive pesticide history, and smoking more than 10 pack-years in Table 2 were derived

Table 1. Variable (mean±SD) values in the three study groups

Variable	PD (n = 235)	MSA (n = 133)	Control (n = 77)	p
Age (years)	67.04±6.13		64.09±10.13	0.057
		65.59±8.05		0.181
Well-water drinking history (years)	20.15±18.74		15.68±20.44	0.080
		19.40±20.09		0.129
1) Urban well water	2.17±7.95		2.27±9.67	0.632
		2.34±8.61		0.735
2) Rural well water	17.97±19.12 [†]		13.33±19.34 [†]	0.018
		17.53±19.51		0.080
Farming duration (years)	6.27±13.68		3.83±10.10	0.223
		7.14±14.37		0.190
Annual frequency of pesticide spraying	1.40±4.45		0.5±1.63*	0.084
		1.09±2.39*		0.037
Smoking (pack-years)	6.07±14.17		8.68±14.32	0.110
		9.30±17.48		0.824

Mann-Whitney test: * $p < 0.05$; [†] $p < 0.01$

Table 2. Risk factors and ORs in the PD and control groups

Risk factor	PD (%)	Control (%)	OR (control = 1) (95% CI)	*p
Well-water drinking history	156 (72.90)	40 (51.95)	1.773 (1.288-2.441)	0.001
Rural well-water drinking history	113 (52.80)	31 (40.26)	1.226 (1.004-1.596)	0.050
Farming duration >5 years	60 (25.75)	11 (14.47)	1.152 (1.022-1.298)	0.041
Pesticide spray frequency >1/year	44 (19.13)	8 (10.67)	1.105 (0.999-1.221)	0.091
Smoking >10 pack-years	46 (19.83)	26 (33.77)	0.826 (0.696-0.981)	0.012

*Chi-square test

from the continuous variables of age (year), duration of well-water drinking (years), duration of farming (years), frequency of pesticide spraying (per year), and smoking (pack-year) in Table 1. Continuous variables were analyzed by the Kruskal-Wallis test, and categorical and continuous variables were analyzed using the chi-square test, *t*-test, and Mann-Whitney test. We used binary logistic regression analysis to identify factors associated with the development of PD or MSA. Statistical significance was accepted for a probability value of $p < 0.05$.

RESULTS

The male/female ratios were 117/118, 68/65, and 38/39 in the PD, MSA, and control groups, respectively. Table 1 summarizes the characteristics of patients, including age, durations of well-water drinking and farming, frequencies of pesticide spraying, and amount of smoking. There was a history of well-water drinking in 156 (73%), 74 (62%), and 40 (52%) of the subjects in the PD, MSA and control groups, respectively. The duration of well-water drinking was greater in the PD group than in the control group (p

< 0.015). The annual frequency of pesticide spraying and total number of the years spent farming were greater in the PD and MSA groups than in the control group ($p < 0.029$ and $p < 0.042$, respectively). Three risk factors were found to be associated with the development of PD: a history of well-water drinking ($p < 0.001$), a history of rural well-water drinking ($p < 0.018$), and farming for more than 5 years ($p < 0.04$). To perform logistic regression analyses, continuous variables were dichotomized into categorical variables using cutoff values close to the median or mean when variables were found to be significantly associated with developing PD. A combined variable was also analyzed, namely the product of farming years and the annual frequency of pesticide spraying, for which its OR for being greater than 30 was 1.089 [95% confidence interval (CI) = 1.004–1.180, $p < 0.086$]. Table 3 summarizes the results of logistic regression analysis performed to identify the possible risk factors for PD and MSA. Smoking more than 10 pack-years prevented the development of PD (OR = 0.311), and each additional year of the age increased the risk of developing PD by 1.059-fold. After adjusting for age, binary logistic regression analysis showed that drinking rural well water for more than 10 years significantly increased the risk of developing PD (by 2.372-fold for each 10 year period), but no significant risk factors

were identified for MSA development.

DISCUSSION

Consistent with previous reports, the consumption of rural well water^{3,5,6} was found to be significantly related to PD in the present study. Koller et al.⁴ concluded that well-water drinking was dependent on rural residency, whereas Zorzon et al.⁷ found that well-water drinking is an independent risk factor for PD. A meta-analysis performed by Priyadarshi et al.⁸ showed the overall risk of drinking well water to developing PD was 1.26 (95% CI = 0.96–1.64). Many studies have examined the relation between PD development and well-water drinking based on the presumption that pesticides can pollute surface water, groundwater, and soil in farming areas. The present study found that only rural well water was found to significantly increase the risk of PD development, with urban well water having no effect. This point supports the notion that pesticides can pollute rural well water. It is also possible that toxins and naturally occurring proteasomal inhibitors other than pesticides also pollute rural well water, and these substances have been occasionally associated with PD.^{20–22}

Table 3. Results of logistic regression analysis

Risk factor	PD			MSA		
	Exp(β)	95% CI	p	Exp(β)	95% CI	p
Sex (for $F = 1$)	0.622	0.300	0.201	0.798	0.304	0.582
Age	1.059	–1.288	0.035	1.017	–1.892	0.337
		1.019			–1.071	
Annual frequency of pesticide spraying	1.099	0.966	0.155	1.095	0.515	0.300
		–1.250			–1.057	
Well-water drinking for > 10 years	1.227	0.659	0.059	0.428	0.206	0.321
		–2.282			–0.888	
1) Urban well water	2.593	0.846	0.096	1.172	0.360	0.792
		–7.944			–3.822	
2) Rural well water	2.372	1.316	0.014	1.481	0.794	0.217
		–4.274			–2.765	
Smoking > 10 pack-years	0.311	0.114	0.010	0.661	0.281	0.309
		–0.643			–1.555	

The development of PD was not correlated with a history of direct pesticide exposure, but it was weakly correlated with a longer history of farming and more frequent use of pesticides. These results are consistent with those of previous studies.¹⁰⁻¹² Based on these diverse results obtained to date, some have argued that PD is not associated with pesticides. Moreover, there have been several reports of a negative correlation between pesticide exposure and PD.^{9,23} However, the meta-analysis conducted by Priyadarshi et al.⁸ on 19 studies published between 1989 and 1999 revealed that the combined OR of pesticides for PD risk was 1.94 (95% CI = 1.49-2.53). The recent comprehensive review of online bibliographic databases by Brown et al.²⁴ revealed a relatively consistent positive association between exposure to pesticides and PD. Korea has experienced rapid socioeconomic change over the past 50 years, changing from an agricultural to an industrial economy. Currently only about 5% of the Korean population is employed in the agricultural sector, and many elderly people now residing in urban areas were once involved in farming and thus were exposed to pesticides. These situations might play a role as a bias in our study.

Smoking has repeatedly been found to be negatively related to PD development.^{7,10,11,13,25} Hernán et al.²⁶ performed a meta-analysis of smoking and the risk of PD, and found that the ORs for PD development were 0.4 for current smokers (95% CI = 0.3-0.5), 0.8 for past smokers (95% CI = 0.7-0.9), and 0.6 for those who had ever smoked (95% CI = 0.5-0.6). Our results concur with these previous observations concerning the protective effect of smoking (>10 pack-years: OR = 0.311, 95% CI = 0.114-0.643).

Choi²⁷ reported a moderate risk of the development of parkinsonism after CO poisoning. Soft coal has been the main source of heating in Korea since the late 1970s, and hence CO poisoning has long been identified as a serious problem. Although CO intoxication might be an environmental risk factor for PD development in Korea, we were unable to verify this due to the small number of cases of CO poisoning in our cohort.

Much less is known about the etiology of MSA

than about PD. Excessive oxidative stress, inflammatory mechanisms, and exposure to heavy metals and toxic materials have been proposed as risk factors for MSA,²⁸⁻³⁰ but these suggestions need to be confirmed. MSA and PD share a common pathogenesis (i.e., they are both synucleinopathies), which suggests that they have common causative factors.

As for PD, the relation between pesticide exposure and the risk of MSA development is controversial, with some studies finding a positive association¹⁵⁻¹⁷ and others a negative association.³¹ In the present study, no relationship was found between environmental risk factors and MSA, and furthermore smoking was not found to affect the risk of MSA development.

It does not appear possible to explain the developments of PD and MSA on the bases of environmental or genetic factors in isolation. However, studies on the interplay between environmental and genetic factors may well provide comprehensive explanations.

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