Environmental, Medical, and Family History Risk Factors for Parkinson's Disease:

A New England-Based Case Control Study

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Controversy persists about the etiology of Parkinson's disease (PD). Pesticides, herbicides, well-water consumption, head injury, and a family history of PD have been reported as risk factors for PD. The purpose of this study was to (1) investigate the impact of environmental factors on PD risk (2) estimate the chronology, frequency, and duration of those exposures associated with PD; and (3) investigate the effects of family history on PD risk. One-hundred and forty PD cases were recruited from Boston University Medical Center. The control group was composed of 147 friends and in-laws of PD patients. Environmental, medical, and family history data were obtained by structured interview from each participant for events recalled prior to PD onset for cases, or corresponding censoring age for controls (mean age = 56 years of age for each group). A traditional stratified analysis, adjusting for birth cohort and sex, was employed. Four factors were associated with increased risk for PD: (1) head injury (OR=6.23, confidence interval [CI]: 2.58-15.07); (2) family history of PD (OR=6.08, CI: 2.35-15.58); (3) family history of tremor (OR=3.97, CI: 1.17-13.50); and (4) history of depression (OR=3.01, CI: 1.32-6.88). A mean latency of 36.5 (SE=2.81) years passed between the age of first reported head injury and PD onset. A mean latency of 22 (SE=2.66) years passed between the onset of the first reported symptoms of depression and onset of PD.

KEY WORDS: Parkinson's disease; risk factors; genetics; family history; head injury

INTRODUCTION

Parkinson's disease (PD) is a progressive movement disorder, involving degeneration of neurons in the substantia nigra, resulting in a decrease in dopamine activity. PD commonly afflicts people later in life, though young onset is possible. Symptoms include tremor, rigidity, bradykinesia, gait and posture disturbance, and both cognitive and emotional changes. Estimates of the prevalence of PD in the United States range from 79 to 187 per 100,000 persons [Martilla, 1989; Mayeux et al., 1995; Zhang and Roman, 1993]. Studies on risk factors and geographical demographics related to PD have been conducted in Canada [Semchuk et al., 1991, 1992, 1993], Kansas [Hubble et al., 1993; Koller et al., 1990], Germany [Seidler et al., 1996], the Pacific Northwest [Butterfield et al., 1993], China [Tanner et al., 1989], and New Jersey [Golbe et al., 1990], but no major studies have taken place in the northeastern United States. Whereas the cause of PD remains unknown, the preponderance of the evidence points toward a multifactorial etiology, most likely involving a genetic susceptibility to the ill effects of an environmental agent or trauma [Kondo et al., 1973; Semchuk et al., 1993].

The genetic patterns of PD appear to follow an autosomal dominant mode of inheritance with reduced penetrance [Lazzarini et al., 1994; Maraganore et al., 1991; Mjönes, 1949]. First-degree relatives of PD cases are from 1.5 to 9.5 times more likely to develop PD than the

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Years of education, smoking, and well-water intake were inversely associated with PD risk. PD was not associated with exposure to pesticides or herbicides. These findings support the role of both environmental and genetic factors in the etiology in PD. The results are consistent with a multifactorial model. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:742–749, 1999. © 1999 Wiley-Liss, Inc.

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first-degree relatives of controls [Alonso et al., 1986; Duvoisin et al., 1969; Marder et al., 1996; Martilla and Rinne, 1976; Martin et al., 1973; Payami et al., 1994; Vieregge and Heberlein, 1995]. Sixteen to 27.5% of PD cases report having a PD-affected relative (isolated tremor excluded) [Kondo et al., 1973; Kurland, 1958; Lazzarini et al., 1994; Martin et al., 1973; Payami et al., 1994; Bonifati et al. 1995]. Family history of PD among first-degree relatives (parents and siblings) has been reported in 6.8 to 16% of PD cases [Lazzarini et al., 1994; Martin et al., 1973; Payami et al., 1994; Semchuk et al., 1993]. Affected siblings have been found for 6 to 7% of PD cases [Lazzarini et al., 1994; Semchuk et al., 1993].

A number of environmental factors have been implicated in the etiology of PD, yet none have been unequivocally identified as causal agents. Findings of geographical and gender differences in PD have supported arguments for an environmental etiology [Tanner and Langston, 1990].

Factors associated with rural living have been reported to increase risk for PD [Butterfield et al., 1993; Golbe et al., 1990; Koller et al., 1990; Morano et al., 1994; Rajput et al., 1986], whereas others have found no association between PD and rural living [Semchuk et al., 1991], farm living or work [Butterfield et al., 1993; Morano et al., 1994; Semchuk et al., 1991; Zayed et al., 1990], or well-water drinking [Semchuk et al., 1991; Zayed et al., 1990]. Rural living also has been associated with a decreased PD risk [Zayed et al., 1990].

Other residential exposures also have been considered. Tanner found an increased risk of PD in China with exposure to printing plants, quarries, and industrial chemicals and a decreased risk with village life [Tanner et al., 1989]. Residence near industry and mining has been associated with a decreased PD risk [Zayed et al., 1990].

Case-control studies found an increased risk for PD with pesticide exposure [Golbe et al., 1990; Hubble et al., 1993; Seidler et al., 1996] and occupational herbicide use [Semchuk et al., 1993, 1992]. Risk for young-onset PD was increased with insecticide exposure, past residency in a fumigated house, and herbicide exposure, but was decreased with farm residency [Butterfield et al., 1993]. Others found no association between PD and pesticide [Zayed et al., 1990] or herbicide exposure [Koller et al., 1990].

Some medical history factors have also been linked to an increased risk for PD including head injury [Seidler et al., 1996; Semchuk et al., 1993; Stern et al., 1991], prior diagnosis of psychoneurosis or psychosomatic illness [Rajput et al., 1987], depression, and family history of neurologic disease [Hubble et al., 1993]. Vitamin E intake may be protective against PD [Golbe et al., 1990] or at least may delay symptoms [Fahn, 1991]. Smoking has been consistently inversely associated with PD. In a review of 46 studies published between 1958 and 1994, most found PD to be less than half as frequent in smokers as in nonsmokers [Morens et al., 1995].

MATERIALS AND METHODS Cases

One hundred forty patients who were diagnosed with PD were examined and followed by neurologists and movement disorder specialists (M.S.-H and R.G.F.) of the Movement Disorder Center at the Boston Medical Center. Every index case met the Ward and Gibb criteria for PD [Ward and Gibb, 1990]. Patients had at least two of the following: tremor, rigidity, and brady-kinesia. They also had one of the following: gait disturbance, postural instability, or hypomimia, and were levodopa responsive. Patients were recruited (by C.A.T.) prior to a regular clinic visit and asked whether they would be willing to participate in this study.

All patients signed a Human Subjects Committee-approved consent form and were interviewed by a trained interviewer (C.A.T.) in person at the clinic. A structured environmental and family history questionnaire was used during the interview. The patient was usually the primary informant; however, if the patient was not oriented to person, place, and time at the time of the interview, a surrogate informant was interviewed. The surrogate informant was the person available who was most knowledgeable about the patient's history; usually this person was the patient's spouse or an adult child.

Controls

Controls were recruited through the PD patient population in the Movement Disorder Center. Controls recruitment was intended to sample a nondisease group of similar age, sex ratio, and socioeconomic status as the cases. Patients were asked whether they had any in-laws or friends over the age of 40 who might be willing to participate as controls in our study. Patients or their spouses were asked to contact those people and inquire about their willingness to participate. The patients or spouses were phoned a week later; cooperation was verified and phone contact was made with 163 potential controls. Twelve declined participation for reasons such as poor health, not interested, or had not been alerted to the study by the patient. Data were obtained for 151 controls. Four never returned the informed consent form and were dropped before analysis. The final number of controls analyzed was 147. The same interview was administered to cases and controls. None of the controls was diagnosed with PD or met the diagnostic criteria for PD. All control interviews were conducted by phone. All control and patient interviews were conducted by the same interviewer (C.A.T.).

Environmental History

Demographic information (sex, marital status, ethnicity, education), residential history, exposure to herbicides and pesticides, and consumption of well water were recorded. Residential history included the names of and number of years spent in each town and state the person had lived in up to the age of PD onset. Each town was identified as being rural (undeveloped or farmland nearby), urban (city, densely populated or industrial), or suburban (any locale not coded rural or

urban). Environmental exposures included pesticides, herbicides, and well water and were recorded as total days of reported lifetime exposure. Years of exposure were computed as days of exposure divided by 365. If subjects indicated that they had been exposed to pesticides or herbicides, they were asked the frequency (once a year, once a month, twice a month, once a week, three times per week, once a day), duration (<1 year, 1-4 years, 5-9 years, 10-19 years, or 20 years or greater) and the initial age of the exposure. The frequency of well-water drinking (one week/year, two weeks/year, one month/year, two months/year, summers only, or every day) was coded according to typically reported usage, whereas duration and age were recorded in the same manner as for pesticides and herbicides exposure.

Medical History

Medical history information was collected for PD onset and diagnosis age, head injuries, smoking, vitamin intake, and history of depression. Head injury was positive if the trauma was severe enough to cause loss of consciousness, blurred or double vision, dizziness, seizures, or memory loss, rather than mere bruising, bleeding, or stitches. Cigarettes were measured in pack years, or the average number of cigarette packs smoked per day times the number of years the individual smoked. Vitamin usage recorded intake of vitamins C, E, beta-carotene, and multivitamins. Vitamin years were coded as the longest continuous use for any vitamin type taken for a minimum of one year. History of depression prior to the onset of PD was recorded. Depression was considered positive if the person reported a period of depression of two weeks duration or longer prior to PD onset. Age of initial depression was recorded. Depressive episodes coinciding with PD diagnosis or onset of PD related symptoms (e.g., tremor, bradykinesia, rigidity) were not coded as positive for depression.

Family History

Information was documented on the subject, all primary relatives (parents, children, full siblings), half-siblings, spouses, and any other relative with neurological or psychiatric impairment. Sex, date of birth, death information (cause of death, age at death, and autopsy information), and relevant medical and exposure information were collected on each relative. Responses were recorded as "yes," "no," or "unsure" for each family member regarding the presence of PD symptoms, other neurologic or psychiatric conditions, and exposures of interest. PD symptoms included tremor, slowness of movement, shuffling gait, postural instability, and facial masking.

Family members of cases and of controls were assigned a diagnostic rating scale (DRS) code based on the number and type of PD symptoms derived from Ward and Gibb criteria [Ward and Gibb, 1990] reported by the proband: $1 = \text{at least two of these signs (tremor, rigidity, bradykinesia) plus one of these signs (gait disturbance, postural instability, hypomimia); <math>2 = \text{at}$

least two of these signs, or one of these signs (tremor, rigidity, bradykinesia) plus one of these signs (gait disturbance, postural instability, hypomimia); 3 = two of these signs (gait disturbance, postural instability, hypomimia); 4 = tremor only; 5 = normal, not a PD case; 6 = other neurologic dysfunction (such as dementia or mental illness).

For analytic purposes, relatives of cases and controls with ratings of 1 or 2 were considered PD-affected for this study, as the relatives in these two categories were considered either probable or possible cases of PD.

Statistical Methods

Data was entered into an ALPHA IV database and analyzed using SAS [SAS Institute, Cary, NC]. Only patient risk factor events occurring before the onset of PD were included in the analyses. Age adjustments were made by stratified analytic methods [Kleinbaum et al., 1982]. Cases and controls were divided into eight birth cohorts of five-year intervals. Born:

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1/1/1915-12/31/1919 (case, n=10; control, n=15); 1/1/1920-12/31/1924 (case, n=18; control, n=20); 1/1/1925-12/31/1929 (case, n=36; control, n=23); 1/1/1930-12/31/1934 (case, n=21; control, n=25); 1/1/1935-12/31/1939 (case, n=20; control, n=19); 1/1/1940-12/31/1944 (case, n=9; control, n=16); 1/1/1945-12/31/1949 (case, n=19; control, n=19); 1/1/1950-12/31/1954 (case, n=7; control, n=10).
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The average age of onset was calculated for the cases in each birth cohort. This age was used as the cut-off for the corresponding control birth cohort so that controls and cases had a similar number of years for reporting exposure events. Thus, only those life experiences for controls that occurred prior to this censoring age were included in the analyses.

Chi-square tests were used to test whether odds ratios differed from unity. *T*-tests were used to compare means for continuous values. Univariate logistic regression was used to calculate odds ratios (OR) for family history (Table I). Multivariate logistic regression was used to calculate adjusted ORs with sex and the birth cohorts treated as categorical variables (Table II).

RESULTS Demographic Characteristics

The majority of PD cases seen in our clinic are male (Table III). On average, cases were interviewed eight years after PD diagnosis. The primary informant was most often the patient (89.3%) and occasionally the spouse (7.9%) or an adult child (2.9%). A secondary informant was available in 63% of the interviews, whereas 36% were conducted with the patient only. One was conducted with a surrogate informant only. Sixty-three percent of the controls were friends or acquaintances of patients, 34% were in-laws (21% were siblings of the patients' spouses; 13% were spouses of the patients' siblings), and 3% were the spouses' inlaws (spouses of the spouses' siblings).

A significantly higher percentage of cases than con-

TABLE I. Family History Information*

Relatives included	DRS codes ^a	% of cases	% of controls	OR	95% CI	<i>P</i> -value
Parents	1 & 2	12.1	5.4	2.4	1.001-5.76	0.050
Siblings	1 & 2	6.4	2.0	3.3	0.87-12.44	0.078
Parents &						
siblings	1 & 2	18.6	6.8	3.1	1.45 - 6.75	0.004
All reported ^b	1 & 2	17.1	7.5	2.6	1.20-5.45	0.015
Parents &						
siblings	1, 2, 3, & 4	30.7	11.6	3.4	1.82 - 6.30	0.0001
All reported ^b	1, 2, 3, & 4	46.4	19.7	3.5	2.09 - 5.96	0.0001

^{*}Univariate logistic regression odds ratios (OR) and confidence intervals (CI). Represents the percentage of cases and controls with respective family members affected.

trols had a family history of PD for all relative groups except siblings. Although the percentage of affected siblings was greater for cases than for controls, the difference was only marginally statistically significant (Table I). Raw numbers of first-degree relatives (mothers, fathers, brothers, and sisters) and second-degree relatives reported to have PD or tremor are presented in Table IV.

The multiple logistic regression analysis revealed that four factors were associated with increased risk for PD. They were (in order of strength) head injury, family history of PD, family history of tremor, and depression (Table II). About 55% of the cases had at least one of these risk factors: 36% had one, 17% had two, and 2% had three. Only 26.5% of the controls had at least one risk factor: 24.5% had one, 2% had two, and none had three. Twenty-five percent of the cases versus 7.5% of the controls had a history of head trauma. Twenty-one percent of the cases versus 11% of the controls reported a history of depression. Family history of PD (DRS = 1 or 2) among first-degree relatives (parents and siblings) was found for 18.6% of the cases and 6.8% of the controls (Table I). Family history of tremor was found for 12.1% of the cases and 3.4% of the controls.

Twenty-nine percent of the cases had a family history of PD or tremor, whereas only 10% of the controls did. Though not statistically significant, male cases were more likely than female cases to have three of the four main risk factors (head injury, family history of PD, or family history of tremor). Female cases were more likely than male cases to report a history of depression (p < 0.035).

For those cases and controls who reported having at least one serious head injury, the average age at which the first head injury occurred was age 16 for cases (n=33) and age 17 for controls (n=11). There was no significant difference in age between the two groups. On average, 36.5 years passed between the time of head injury and the age of PD onset.

Subjects who reported depression experienced their first depressive episode a mean of 22 years before PD onset for cases (n=29) and 19 years earlier than censoring age for controls (n=16). There was no significant difference in depression onset age between the two groups.

The remaining risk factors (education, urban, suburban, and rural living, pesticides, herbicides, well water, smoking, and vitamin intake) were measured as con-

TABLE II. Logistic Regression Analyses of Risk Factors*

	Birth cohort and sex adjusted			Full model			
Risk factors	OR1	95% CI	P value	OR2	95% CI	P value	
Head injury	5.09	2.33-11.09	0.0001	6.23	2.58-15.07	0.0001	
Family HX: PD	3.94	1.74 - 8.94	0.001	6.08	2.35 - 15.69	0.0002	
Family HX: tremor	4.42	1.50 - 13.06	0.007	3.97	1.17 - 13.50	0.027	
Depression	2.46	1.25 - 4.85	0.01	3.01	1.32 - 6.88	0.009	
Years of:							
Education	0.87	0.80 - 0.96	0.003	0.79	0.71 - 0.88	0.0001	
Urban living	1.01	0.99 - 1.02	0.36	1.05	0.99 - 1.12	0.12	
Suburban living	0.99	0.98 - 1.01	0.28	1.04	0.98 - 1.11	0.20	
Rural living	1.01	0.98 - 1.03	0.60	1.07	0.99 - 1.15	0.06	
Pesticide	1.04	0.93 - 1.17	0.48	1.02	0.90-1.17	0.73	
Herbicide	1.03	0.76 - 1.40	0.85	1.06	0.68 - 1.65	0.81	
Well water	0.96	0.93 - 0.99	0.02	0.93	0.88 - 0.98	0.003	
Smoking (pack/yrs)	0.99	0.98 - 0.998	0.02	0.98	0.96 - 0.99	0.001	
Vitamins	1.01	0.99 – 1.04	0.28	1.02	0.99-1.06	0.26	

^{*}Multivariate odds ratio (birth cohort and sex adjusted only = OR1; birth cohort, sex, and all other covariates adjusted = OR2); HX = history.

^aDRS codes of reported family members based on proband reporting. DRS 1 = at least two of these signs (tremor, rigidity, bradykinesia) plus one of these signs (gait disturbance, postural instability, hypomimia). DRS 2 = at least two of these signs, or one of these signs (tremor, rigidity, bradykinesia) plus one of these signs (gait disturbance, postural instability, hypomimia). DRS 3 = two of these signs (gait disturbance, postural instability, hypomimia). DRS 4 = tremor only.

^bAll relatives: parents, siblings, grandparents, aunts, uncles and cousins, reported affected.

TABLE III. Description of Subjects

		Cases $(N = 140)$	Controls $(N = 147)$
Sex	Female Male	37% (n = 52) $63% (n = 88)$	$ 39\% (n = 57) \\ 61\% (n = 90) $
Interview Age	Mean Range	66.2 ± 10.3 $(31-88)$	66.9 ± 10.8 $(42-88)$
Diagnosis age	Mean Range	57.7 ± 10.6 (0–82)	— —
Onset age/ censoring age	Mean Range	56.0 ± 10.7 $(26-82)$	55.6 ± 9.9 Eight 5-year birth cohorts (1915 to 1954)

tinuous variables by years of exposure (Table II). There was no difference between the case and control groups for birth cohort. A cohort effect was observed for suburban years, urban years, and smoking years. Residential cohort effects were observed because older cohorts had more years to live in their respective environments than the younger cohorts. For smoking years, the 1920-1924 birth cohort smoked significantly longer than the older and the younger cohorts. Analysis of variance, adjusting for cohort and sex, showed education years (p <0.003), smoking (pack) years (p <0.02), and years drinking well water (p <0.02) to be significantly greater in controls than in cases.

Among the PD cases, a correlation was found between the number of years a patient took vitamins before PD onset and both the age at onset $(r=0.45,\ p<0.004)$ and age at diagnosis of disease $(r=0.43,\ p<0.007)$. PD cases who took vitamins for a longer period of time had an older onset than those who took vitamins for less time. The correlation is still significant after adjusting for the age at which vitamin intake began.

DISCUSSION

We found head injury, depression, family history of PD, and family history of tremor to be risk factors for PD. Among the medical history variables studied, head injury (OR = 6.23) and depression (OR = 3.01) were the strongest risk factors, with both occurring well before PD onset. Head injury occurred a mean of 37 years

before PD onset and depression a mean of 22 years earlier. Similar results have been reported previously for head injury [Factor and Weiner, 1991; Seidler et al., 1996; Semchuk et al., 1993; Stern et al., 1991]. Factor and Weiner reported a 37.7-year time span between head injury and PD onset, though cases did not differ significantly from controls after adjusting for sex [Factor and Weiner, 1991]. Semchuk reported a 38.9-year latency period, with head injury occurring at a mean age of 19.1 and PD onset at a mean age of 58 [Semchuk et al., 1993]. Stern found a 19.8-year time difference between PD onset and age of the most recent head injury [Stern et al., 1991].

Depression has long been considered a common clinical feature co-occurring with PD [Levin and Katzen, 1995; Mayeux et al., 1981]. Some studies have estimated the prevalence of depression at 47% in patients with PD [Dooneief et al., 1992; Mayeux et al., 1981]. While much attention has been paid to the concept of a 'premorbid Parkinsonian personality' [Eatough et al., 1990; Jimenez-Jimenez et al., 1992; Paulson and Dadmehr, 1991; Poewe et al., 1983, 1990; Sands, 1942; Todes and Lees, 1985], little has been documented regarding depression as a possible risk factor for PD [Hubble et al., 1993]. We found a latency of 22 years between the first reported depressive episode of twoweek duration or longer and the onset of PD. These findings support the possibility that depression precedes the onset of PD by many years.

Family history of PD (OR = 6.08) and of tremor (OR=3.97) in parents and siblings were also strong predictors of PD (Table II). Cases were consistently more likely than controls to have an affected family member: roughly three to four times more likely in birth cohort and sex adjusted analyses and six times more likely in birth cohort, sex, and other risk factoradjusted analyses (Table II). Many studies have found family history of PD [Alonso et al., 1986; Duvoisin et al., 1969; Lazzarini et al., 1994; Marder et al., 1996; Martilla and Rinne, 1976; Martin et al., 1973; Payami et al., 1994; Seidler et al., 1996; Semchuk et al., 1993; Vieregge and Heberlein, 1995; Wang et al., 1993] and family history of tremor [De Michele et al., 1996; Jankovic et al., 1995; Morano et al., 1994; Vieregge, 1994] to be major risk factors for PD and with odds ratios of

TABLE IV. Family Members Affected (Raw Numbers)

	Cases $(n = 140)$			Controls $(n = 147)$		
Relatives	DRS = 1 or 2	DRS = 3 or 4	Total reported	DRS = 1 or 2	DRS = 3 or 4	Total reported
Number of First-Degree Relatives Affected						
Mothers	10	8	140	5	2	147
Fathers	7	11	140	4	4	147
Sisters	7	7	201	0	0	152
Brothers	6	7	186	3	1	167
Total parents & siblings	30	33	667	12	7	613
•	(4.5%)	(4.9%)		(2.0%)	(1.1%)	
Number of Second-Degree Relatives Affected						
Maternal lineage*	15	10	25	7	2	9
Paternal lineage*	12	2	14	5	2	7
Total second degree relatives	27	12	39	12	4	16

^{*}Second- and third-degree relatives (aunts, uncles, grandparents, cousins)

similar magnitude. We find a similar risk to parents and siblings for PD, which is consistent with an autosomal dominant mode of inheritance with reduced penetrance. Although the study did not involve a systematic follow-up of PD-affected relatives, we are conducting a genetic linkage study of PD-affected sibling pairs. Of the 13 reported affected siblings (Table I, DRS 1 and 2), 5 are deceased and could not be examined, 3 declined examination or were lost to follow-up, and the remaining 5 were confirmed to have PD on examination. None of the examined siblings failed to meet PD diagnostic criteria.

It was surprising that greater education had a "protective" effect for PD, though the educational difference between cases (15 years) and controls (16 years) was just 1 year. While no other studies report this finding, they may have matched for educational status and not assessed the effect education may have on disease onset. A similar relationship has been reported between education and Alzheimer's disease, where those with less education are at greater risk for dementia [Stern et al., 1994]. These findings have been disputed, however, after adjusting for age and birth cohort effects [Cobb et al., 1995]. Our control selection methodology may have introduced a bias for more education among controls. Since patients were asked to identify in-laws and friends who "might be willing to serve as a control in this study," they may have inadvertently chosen those who would most likely understand, and therefore be more willing to participate, in the study. Thus, controls may have been selected unwittingly for being more educated.

Past studies have implicated factors associated with both rural living [Butterfield et al., 1993; Golbe et al., 1990; Granieri et al., 1991; Koller et al., 1990; Morano et al., 1994; Rajput et al., 1986; Thiessen et al., 1990] and industrial toxins [Tanner et al., 1989] in the etiology of PD. In the residential and toxic exposure components of our study, we assessed whether rural living, urban living, or factors related to either predisposed people to PD. Although significant differences were not seen in any of the residential groups, cases spent more years in rural and urban areas, while controls lived more often in the suburbs. This finding neither confirms nor disputes the hypothesis that residential environment may be associated with PD. Others have found no association between PD and rural living [Semchuk et al., 1991]. The majority of past studies reporting an association between rural living and PD have been performed in the midwestern United States [Hubble et al., 1993; Koller et al., 1990] or Canada [Semchuk et al., 1991, 1992, 1993]. PD cases ascertained in the northeastern United States may have different risk factors. It is possible that controls, being friends, in-laws, or residential acquaintances of the cases, were overmatched with the cases for residential exposures. Controls may have shared similar residential living experiences (environment, toxic exposures, water usage) with the cases over some portion of their lifetime. The roles of pesticides, herbicides, and well water in the etiology of PD have been unclear: some have found one or more of these factors to be associated with increased PD risk [Barbeau et al., 1987; Butterfield et al., 1993; De Michele et al., 1996; Hubble et al., 1993; Koller et al., 1990; Morano et al., 1994; Seidler et al., 1996; Semchuk et al., 1992, 1993], whereas others have found no association [Seidler et al., 1996; Semchuk et al., 1991; Zayed et al., 1990] or even decreased risk [Wang et al., 1993]. While none were significant risk factors in this study, reported pesticide exposure was slightly increased in cases, herbicides were equal in both groups, and well-water use was significantly more common in controls. These factors are extremely difficult to assess retrospectively for an entire lifetime. Potential dangers of household use of pesticides and lawn sprays have only recently been in the general public's awareness. Defining appropriate inclusion criteria for assessing well-water usage and toxicity is a challenging task. A number of subjects commented that they used a well but: "it was very deep," "it was artesian," "it was town well water," or "it checked out negative for chemical contamination." For this analysis all varieties of well water were combined into one category, which may impede our ability to detect risk associated only with a subset of exposures.

We found that controls smoked an average of six pack-years more than cases. In a review of over 46 studies on the association between PD and smoking, the majority reported smoking to have a protective effect [Morens et al., 1995]. Several theories have arisen to explain this observation: the onset of PD may reduce smoking [Mayeux et al., 1994] or smokers may be protected due to a decrease in MAO B activity and a consequent increase in dopamine activity [Fowler et al., 1996].

In this study, PD patients reporting a longer duration of vitamin use had a significantly older mean age of onset than patients who reported less vitamin use. We found no difference in the frequency of vitamin use for patients and controls and therefore, while vitamins did not appear to prevent PD, they were associated with delay in the onset of disease among cases who took them. A past study found antioxidant use was associated with delayed need for levodopa [Fahn, 1991]. The effect of vitamin use on PD risk and the association with disease onset deserves additional attention.

The majority of PD cases seen in our sample, roughly 63%, were men. In the United States, Norway [Tandberg et al., 1995], Germany [Trenkwalder et al., 1995], and other countries, PD is more common among men than women; however, this is not consistently found worldwide. For example, in Italy PD is more common in women than men [Beghi et al., 1994]. Sex differences were apparent in risk factor analysis as well. In our study, male cases were more likely to report a head injury, family history of PD, or family history of tremor, whereas female cases were more likely to report depression.

Case recruitment from a tertiary academic medical center and hospital-based neurology clinic was a relatively simple process. However, recruiting a suitable control group was problematic because the population that gave rise to the cases was not well-defined. Thus, no single community or geographic region could be defined as a catchment area. Since the referral sources for the clinic are diverse, in-laws and friends were

deemed to be representative of the "population" that gave rise to our cases. To minimize overmatching on residential and environmental factors, spouses were not chosen as controls.

Subjects were interviewed in the most effective and feasible manner for each group. Cases were interviewed in person as they were available at the clinic and because disease symptoms would have interfered with a long phone interview. Controls were interviewed by phone because it was not feasible to arrange for them to travel to the medical center for an interview. These different interview methods may create a systematic bias if the collection of information by telephone changes the manner in which study participants respond to the inquiry. Nevertheless, the length of the interview by the two methods was monitored and similar, and the extent of detail gathered for exposures was similar.

The potential for recall bias has been raised in the case control studies of PD [Semchuck and Love, 1995]. PD patients may attribute greater significance to past events such as head traumas and perceived environmental exposures than will control subjects. The presence of relatives with PD might also be recalled more frequently by patients than controls. However, Maraganore and his colleagues [Maraganore et al., 1996] found no evidence for recall bias for family history of PD and Uitti et al. [1997] found that PD patients underreported the presence of PD in their relatives. These studies suggest that the self-report methods for collection of PD family history do not result in recall bias or overestimation of PD-affected relatives.

The etiological precursors of PD have proven to be difficult to identify. One method to verify the role of putative causative agents is to examine their association with disease in different geographic regions. The present study found that reported events of head trauma, and family history of PD or tremor were most strongly associated with PD, whereas cigarette smoking was associated with decreased PD risk. The combined finding of familial clustering of PD together with environmental risk factors supports a multifactorial disease etiology.

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