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Risk factors for Parkinson's disease may differ in men and women: An exploratory study

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Abstract

Although several environmental and genetic risk or protective factors have been associated with Parkinson's disease (PD), their interactions overall and in men and women separately remain unknown. We used the medical records-linkage system of the Rochester Epidemiology Project to identify 196 subjects who developed PD in Olmsted County, MN, from 1976 through 1995. Each incident case was matched by age (± 1 year) and sex to a general population control. We considered the following 12 risk or protective factors: personal history of head trauma, pesticide use, immunologic diseases, anemia, hysterectomy (in women only), cigarette smoking, coffee consumption, and education; and family history of parkinsonism, essential tremor, dementia, or psychiatric disorders. We used recursive partitioning analyses to explore interactions overall and in men and women separately and used logistic regression analyses to test for interactions. In the overall group, we observed the independent effects of anemia, lack of coffee consumption (never vs. ever), and head trauma; however, the findings were different in men and women. In men, we observed the independent effects of lack of coffee consumption (never vs. ever), head trauma, and pesticide use, and a suggestive synergistic interaction between immunologic diseases and family history of dementia. By contrast, in women, anemia was the most important factor and we observed a suggestive synergistic interaction between anemia and higher education. Risk factors for PD and their interactions may differ in men and women.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease of unknown etiology with higher incidence in men than in women (Baldereschi et al., 2000; Bower et al., 1999; Tanner and Goldman, 1996; Van Den Eeden et al., 2003). Although several environmental and genetic risk or protective factors have been studied one-at-a-time in men and women combined (de Lau and Breteler, 2006; Elbaz and Moisan, 2008), their interactions have

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rarely been studied in men and women separately (Ross and Smith, 2007). The discovery of joint effects may help to clarify the etiology and pathophysiology of PD. In addition, combinations of risk factors may identify men or women who are at high risk of developing PD many years before the onset of motor manifestations.

We took advantage of several case-control studies conducted in Olmsted County, MN, and published over the past 10 years to explore possible combinations of risk or protective factors for PD using recursive partitioning techniques (Arabia et al., 2007; Benedetti et al., 2000; Benedetti et al., 2001; Bower et al., 2006; Bower et al., 2003; Frigerio et al., 2005; Frigerio et al., 2006; Rocca et al., 2007a; Rocca et al., 2007b; Rocca et al., 2004; Savica et al., 2009b). In addition, we performed formal tests of interaction for the joint effects suggested by recursive partitioning. We conducted analyses in the overall group and in men and women separately.

Methods

Cases

We used the medical records-linkage system of the Rochester Epidemiology Project to identify all subjects residing in Olmsted County, MN, who developed PD from 1976 to 1995. Details about the study population and the identification of incident cases were reported elsewhere (Bower et al., 1999; Melton, 1996; St Sauver et al., 2012; St Sauver et al., 2011). Our diagnostic criteria included two steps: the definition of parkinsonism as a syndrome and the definition of PD within the syndrome.

Parkinsonism was defined as the presence of at least two of four cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. PD was defined as the presence of parkinsonism with all three of the following criteria: 1) No other cause (e.g., repeated stroke with step-wise progression; repeated head injury; history of encephalitis; neuroleptic treatment within 6 months before onset; hydrocephalus; brain tumor); 2) No documentation of unresponsiveness to levodopa at doses of at least 1 gm/day in combination with carbidopa (applicable only to patients who were treated); 3) No prominent or early (within 1 year of onset) signs of more extensive nervous system involvement not explained otherwise (e.g., dementia or dysautonomia) (Bower et al., 1999). Our clinical classification of patients with PD through medical records review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere (Elbaz et al., 2002). Onset of PD was defined as the year in which a cardinal sign of PD was first noted by the patient, by family members, or by a care provider (as recorded in the medical record).

Controls

Each case was individually matched by age (± 1 year) and sex to a general population control residing in Olmsted County and free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). The list of all county residents from which potential controls were randomly drawn was provided by the records-linkage system (Melton, 1996; St Sauver et al., 2012; St Sauver et al., 2011). This list has been shown to be complete by comparison with a random-digit-dialing telephone sample and with the census (Melton, 1996; St Sauver et al., 2012; St Sauver et al., 2011). Records of potential controls were reviewed by a neurologist to exclude the presence of PD, other types of parkinsonism, or tremor of any type before or during the index year. The presence of dementia or other neurologic diseases was not an exclusion criterion. Our exclusion of parkinsonism in controls through medical record review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere (Elbaz et al., 2002).

Additional details about the methods of these studies can be found elsewhere (Elbaz et al., 2002).

Measurement of risk factors

This study used data from a series of case-control studies of 12 genetic or environmental risk or protective factors for PD considered one-at-a-time. In particular, we considered the following eight risk or protective factors from the personal history of cases and controls: head trauma (Bower et al., 2003), pesticide use (Frigerio et al., 2006), immunologic diseases (Bower et al., 2006), anemia (Savica et al., 2009b), hysterectomy (only in women) (Benedetti et al., 2001), cigarette smoking, coffee consumption, and education (Benedetti et al., 2000; Frigerio et al., 2005). In addition, we considered the following four risk factors from studies of first-degree relatives of cases and controls: family history of parkinsonism (Rocca et al., 2004), essential tremor (Rocca et al., 2007b), dementia (Rocca et al., 2007a), and psychiatric disorders (anxiety and depression) (Arabia et al., 2007). Table 1 shows the results of these 11 studies overall and in men and women separately. More extensive details about data collection and the definitions for each risk or protective factor were reported in the original papers (Arabia et al., 2007; Benedetti et al., 2000; Benedetti et al., 2001; Bower et al., 2006; Bower et al., 2003; Frigerio et al., 2005; Frigerio et al., 2006; Rocca et al., 2007a; Rocca et al., 2007b; Rocca et al., 2004; Savica et al., 2009b). Only brief definitions are included in Table 1.

Information for the eight risk or protective factors from the personal history of cases and controls was abstracted from the full set of medical records available in the records-linkage system of the Rochester Epidemiology Project (Melton, 1996; St Sauver et al., 2012; St Sauver et al., 2011). Information from the medical records was abstracted by a specifically trained nurse in some of the studies (Bower et al., 2006; Bower et al., 2003) and by a physician in other studies (Benedetti et al., 2000; Benedetti et al., 2001; Frigerio et al., 2005; Frigerio et al., 2006; Savica et al., 2009b). Details about the reliability and validity of the risk or protective factors information are given in the original reports (Benedetti et al., 2000; Benedetti et al., 2001; Bower et al., 2006; Bower et al., 2003; Frigerio et al., 2005; Frigerio et al., 2006; Savica et al., 2009b).

Information about the four family history variables was collected as part of an extensive familial aggregation study. The presence of diseases among first-degree family members of patients with PD and controls was assessed using a family study method whereby we constructed detailed pedigrees and each relative was studied independently (to the fullest extent possible). The study involved telephone screening interviews, examination of relatives who screened positive, abstraction of medical records in a records-linkage system, abstraction of medical records from outside of the records-linkage system, and review of death certificates (Elbaz et al., 2003; Rocca et al., 2005). Extensive details about the results of our study were provided elsewhere (Arabia et al., 2007; Rocca et al., 2007a; Rocca et al., 2007b; Rocca et al., 2004). For each case or control, we collapsed the full pedigree information into a dichotomous variable labeled family history positive if at least one first-degree relative was affected by the disease of interest.

Additional case-control studies conducted in the same Olmsted County population showed an association of PD with a personal history of anxiety disorders, depressive disorders, and constipation (Savica et al., 2009a; Shiba et al., 2000). However, these associated conditions may be interpreted as early manifestations of the PD process rather than causal factors; therefore, they were not considered in the present study (Savica et al., 2010).

Analyses

All risk or protective factors were defined dichotomously (yes/ever vs. no/never) and analyses involved two phases. In phase 1 we explored data using recursive partitioning to identify possible interactions, and in phase 2 we tested statistical significance for the interactions suggested by phase 1 using logistic regression analyses. We performed analyses overall and for men and women separately.

Specifically, in phase 1, we employed the function RPART written in the S-Plus® software (Insightful Corporation, Seattle, WA) to construct a classification tree (Zhang and Bonney, 2000). Recursive partitioning is a nonparametric technique that produces a classification tree in which subjects are categorized in exclusive subgroups according to a set of predictor variables. The Gini Diversity Index was used to examine all possible splits of the full group of subjects (root node; oval shape) and to identify the factor at each level that reached the greatest purity, i.e., that maximally discriminated PD status versus control status (Breiman L., 1984). A subgroup is completely pure when it contains only cases or controls, and is completely impure when it contains cases and controls in the same proportion as the root node. Each binary split yielded two subgroups (descendant nodes; oval shape), one that contained a relatively high proportion of cases (splitting to the right) and the other that contained a relatively high proportion of controls (splitting to the left). Each descendant node was examined for possible further splits until no nodes could be further split.

At the end of the recursive partitioning process, the initial tree was pruned using the technique of cross-validation and was restricted to splits with a minimum complexity parameter of 0.02 or greater (Nelson et al., 1998). The end results of the recursive partitioning process were terminal nodes representing combinations of risk factors associated with increased or decreased likelihood of PD (terminal nodes; rectangular shape). Because recursive partitioning is exploratory and does not test specific hypotheses, concerns about multiple comparisons do not apply.

In phase 2, we used logistic regression models in the full sample of cases and controls to test for the interactions of risk factors suggested by phase 1. Associations were measured using odds ratios (ORs) and their 95% confidence intervals (95% CIs). We used both the multiplicative and the additive models of interaction to detect synergistic and antagonistic joint effects (Szklo and Nieto, 2007). Additive interaction was assessed using a likelihood ratio test comparing the full joint effect model to a model with constrained parameters ($OR_{\text{factor A only}} + OR_{\text{factor B only}} - 1 = OR_{\text{joint effect of factor A and B}}$). All statistical tests were performed at the standard two-tailed alpha level of 0.05 using SAS® (SAS Institute, Cary, NC) and S-Plus®. Interactions that were shown by recursive partitioning but did not reach conventional statistical significance in logistic regression models were considered suggestive.

Results

We included 196 case-control pairs for a total of 392 individuals as described in detail elsewhere (Elbaz et al., 2002). Among the cases, 121 (61.7%) were men and 75 (38.3%) were women; the median age at onset of PD was 71 years (range 41 to 97 years) overall, 70 years in men (range 41 to 91 years), and 72 in women (range 44 to 97 years). The distribution by age and sex was similar in controls due to the matched design. Table 1 summarizes the results published from this case-control sample for 12 risk or protective factors considered one-at-a-time (12 factors published in 11 papers).

Figure 1 shows the optimally pruned tree for men and women combined. The tree showed the effect of anemia, lack of coffee consumption (never vs. ever), and head trauma as

independent risk factors. Subjects who had at least one of these three risk factors (composite exposure variable) had nearly a three-times greater risk of PD (OR 2.74; 95% CI 1.82–4.13). The recursive partitioning analysis did not reveal any potential interactions.

Figure 2 shows the optimally pruned trees for men and women separately. In the tree for men, lack of coffee consumption (never vs. ever), history of head trauma, and pesticide use were independent but relatively rare risk factors. Subjects who had at least one of these three risk factors (composite exposure variable) had nearly a five-times greater risk of PD (OR 5.28; 95% CI 2.67–10.43). In the absence of these three risk factors, a personal history of immunologic diseases was the strongest risk factor (Fig. 2). Guided by the recursive partitioning analysis, we investigated the possible interaction of immunologic diseases with family history of dementia. Men with both immunologic diseases and family history of dementia had a significantly increased risk of PD compared with men without either factor (OR 2.81; 95% CI 1.13–6.98). However, the formal test for a synergistic interaction was not significant using either an additive or a multiplicative scale (data not shown).

The tree for women showed no lifestyle or occupational risk factors for PD but suggested a possible joint effect between anemia and higher education (> 8 years vs otherwise) (Fig. 2). In logistic regression models, women with higher education who experienced anemia had a significantly increased risk of PD compared to women without either factor (OR 4.71; 95% CI 1.61–13.72). However, the formal test for a synergistic interaction was not significant using either an additive or a multiplicative scale (data not shown).

Discussion

Our findings suggest a difference in the pattern of risk or protective factors for PD in men and women. In men, the most important risk factors were lifestyle and occupational factors acting independently. By contrast, in women, none of the lifestyle or occupational factors was important, and anemia was the primary risk factor. A couple of different factor-to-factor interactions in men and women were suggested by our recursive partitioning exploratory analyses but did not reach statistical significance.

Our findings of different risk or protective factors in men and women are consistent with differences in incidence, clinical characteristics, or prognosis in men and women that were shown in previous studies. Several authors described a twofold higher risk of PD in men as compared with women (Baldereschi et al., 2000; Bower et al., 1999; Tanner and Goldman, 1996; Van Den Eeden et al., 2003) and a meta-analysis confirmed the sex difference in risk of PD (Wooten et al., 2004). Some authors also described a difference in clinical characteristics between sexes. Women had more advanced clinical symptoms of PD at onset (Rajput et al., 1984) and had higher frequency of postural instability, urinary incontinence, pain, depression, and xerostomia when compared with men (Ehrt et al., 2007; Rajput et al., 1984; Scott et al., 2000). However, there was no difference in cardinal signs (Scott et al., 2000) and in mortality (Marras et al., 2005) between the two sexes.

Similarly, other authors reported a lower incidence, a delayed onset of symptoms, a lower frequency of tremor, and a better clinical prognosis in women when compared with men (Haaxma et al., 2007). Another study reported that women had a delayed referral to a movement disorder specialist compared with men (Saunders-Pullman et al., 2011b).

We propose three hypothetical mechanisms to explain the men to women differences in risk or protective factors for PD. The first two mechanisms are based on a different susceptibility of the brain of men and women to PD due to hormonal, genetic, or developmental differences. The third mechanism postulates that the brain susceptibility is similar in men

and women but men are more frequently exposed to social or behavioral risk factors. These three mechanisms are not mutually exclusive and additional mechanisms can be postulated.

The first mechanism is a direct protective effect of hormonal or genetic factors in women compared with men. Being a man might be a direct risk for PD because of lack of the neuroprotective effect of estrogen or because some genes on the X or Y chromosomes are involved in the susceptibility to PD. Several mechanisms of estrogen protection on the nigrostriatal pathway have been demonstrated in animal models using selective neurotoxins (Callier et al., 2000; Datla et al., 2003; Dluzen, 1997; Gajjar et al., 2003; Gao and Dluzen, 2001; Gillies et al., 2004; Miller et al., 1998; Rocca et al., 2008; Sawada and Shimohama, 2003). Interestingly, estrogen has opposite effects on the nigrostriatal pathway in male mice (harmful) and female mice (protective) (Gillies and McArthur, 2010). Estrogen has been found to also protect the dopaminergic neurons in primate animals (Leranth et al., 2000). Unfortunately, the clinical and epidemiological evidence remain conflicting (Rocca et al., 2008). In support of a neuroprotective role of estrogens, some authors have reported an increased risk of parkinsonism in women who underwent bilateral oophorectomy before menopause (Benedetti et al., 2001; Rocca et al., 2008).

Genetic factors for PD susceptibility may involve genes located on the sex chromosomes or on the remaining chromosomes. Genetic susceptibility variants for PD have been identified on chromosome X and these variants may explain the difference in PD risk between sexes (Pankratz et al., 2002). In addition, a study conducted in Israel reported an over-representation of PD in Jewish women who carry a LRRK2 mutation (G2019S) as compared with men with the same mutation (Orr-Urtreger et al., 2007).

The second mechanism is a dimorphic early life development of the nigrostriatal pathway and of the overall brain in men and women. Several authors have described a sex difference in the development of brain networks, pathways, and neural connections (Allen et al., 2003; Baron-Cohen et al., 2005; Baxter et al., 2003; Braeutigam et al., 2004; Dewing et al., 2006; Gillies and McArthur, 2010; Pakkenberg and Gundersen, 1997; Shaywitz et al., 1995). For example, the corpus callosum is smaller in men than women (Allen et al., 2003), and men have more densely packed neurons (Pakkenberg and Gundersen, 1997). These findings suggest a pattern of increased local connectivity and decreased interhemispheric connectivity in men (Baron-Cohen et al., 2005). Physiological studies have confirmed a lower interhemispheric connectivity in men (Baxter et al., 2003; Braeutigam et al., 2004; Shaywitz et al., 1995). In summary, the brain may have a sex-dependent dimorphic development that modifies its susceptibility to environmental agents.

The third mechanism is a different exposure of men and women to social and behavioral risk or protective factors. For example, men can be more exposed than women to some environmental risk factors that lead to PD such as head trauma (Bower et al., 2003) and pesticides (Frigerio et al., 2006) because of occupational or recreational differences. Men are more likely to have jobs that require strenuous physical labor and risk of trauma (Bower et al., 2003; Frigerio et al., 2005). Men are more likely to handle herbicides or other pesticides as part of farming activities (Frigerio et al., 2006). Men are also more likely to engage in contact sports and high risk recreational activities such as mountain climbing, surfing, and martial arts (Bower et al., 2003). By contrast, anemia is more common in women than in men, it may be related to gynecological conditions such as menstrual cycle irregularities or uterine fibromas, and may lead to hysterectomy (Benedetti et al., 2001; Savica et al., 2009b). However, anemia remained associated with PD after adjustment for hysterectomy in our original study, suggesting that hysterectomy is not a confounding factor (Savica et al., 2009b). Behavioral or environmental exposures may have simple or complex interactions with genetic variants in men and women, and genetic and environmental factors may

contribute in different proportion to the risk of PD in men and women (Saunders-Pullman et al., 2011a).

Our study has a number of strengths. First, we took advantage of a well-established population-based case-control series from Olmsted County, MN, to study 12 risk or protective factors in the same population. Although other studies have used the recursive partitioning technique to explore risk factors in PD (Maraganore et al., 2003a; Maraganore et al., 2003b), our study was more extensive and involved both genetic (family history) and non-genetic risk factors. Second, the recursive partitioning technique may uncover interactions that may be missed by logistic regression analyses (less restrictive statistical assumptions), is well suited to handle large data sets, and can handle missing data better than traditional multivariate analyses (Nelson et al., 1998). Moreover, the cross-validation approach reduced the chance of making a type 1 error.

Our study also has a number of limitations. First, recursive partitioning is an exploratory and hypothesis-generating method and the interactions revealed may not correspond to true biological phenomena. Therefore, our findings await replication by other studies. Second, we explored mostly lifestyle and occupational risk or protective factors, and we had only limited information on genetic factors. We used the familial aggregation of PD and other neurological conditions to indicate genetic susceptibility; however, we did not have information on specific genetic variants (single nucleotide polymorphisms or other genetic markers).

Third, we only included in our analyses 12 risk or protective factors that have been found to be associated with PD. Therefore, we may have excluded some relevant factors only because they have not been studied adequately or because the findings have not yet been replicated. Fourth, some risk or protective factors may not have been reported thoroughly in the medical records and may have been missed. However, the underestimation of exposure should be similar for cases and controls (non-differential misclassification). Fifth, the study population of Olmsted County, MN, is primarily Caucasian of northern and central European descent. Therefore, our findings may not be generalizable to other populations with different ethnic or social characteristics (Melton, 1996; St Sauver et al., 2012). Finally, the sample size of our case-control analyses had limited power when considering men and women separately. The statistical power was lower for women than for men because of the lower incidence rate of PD in women (Bower et al., 1999). Therefore, we may have failed to show important associations with risk or protective factors with low frequency in the population.

In conclusion, our study suggests that PD is multifactorial at the individual level and heterogeneous at the population level. This heterogeneity may be further complicated by differences between men and women. These differences may open new lines of research to clarify the etiology and pathophysiology of PD. However, because of the exploratory nature of our analyses, our findings await replication in other studies.

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Highlights

- The risk and protective factors for Parkinson's disease may differ in men and women
- Lack of coffee consumption, head trauma, and pesticide use may be important in men
- Anemia and higher education may be important in women
- The interactions explored in this study were different in men and women

Fig. 1.

Risk and protective factor for Parkinson's disease: optimally pruned recursive partitioning tree for men and women combined. In each node, we show the number of controls (left) and the number of cases (right) separated by a slash. In the terminal nodes, we also show the percent of controls (left splits) or of cases (right splits).

Men **Women** **Fig. 2.**

Risk and protective factors for Parkinson's disease: optimally pruned recursive partitioning trees for men (upper panel) and women separately (lower panel). In each node, we show the number of controls (left) and the number of cases (right) separated by a slash. In the terminal nodes, we also show the percent of controls (left splits) or of cases (right splits).

Risk or protective factors for PD in 11 case-control studies conducted using the same sample in Olmsted County, MN.

Table 1

Reference	Factor studied ^a	Definition	Men		Women		Overall	
			OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Personal history risk factors ^b								
Benedetti et al., 2000	Coffee consumption	From medical records	0.06	(0.01-0.5)	1.0	(0.4-2.9)	0.4	(0.2-0.8)
	Cigarette smoking ^c	From medical records	0.8	(0.5-1.4)	0.6	(0.3-1.2)	0.7	(0.5-1.1)
Benedetti et al., 2001	Hysterectomy	Without bilateral oophorectomy	-	-	3.4	(1.1-10.8)	-	-
Bower et al., 2003	Head Trauma	With loss of consciousness, post-traumatic amnesia, neurologic signs of brain injury, or skull fracture	6.0	(1.3-26.8)	1.0	(0.1-16.0)	4.3	(1.2-15.2)
Frigerio et al., 2005	Education	>8 years vs. otherwise	2.0	(0.9-4.3)	2.0	(0.8-5.3)	2.0	(1.1-3.6)
Frigerio et al., 2006	Pesticide use	Via telephone interview. Related or unrelated to farming	2.4	(1.1-5.4)	0.6	(0.2-1.9)	1.5	(0.8-2.9)
Bower et al., 2006	Immunologic disease	Asthma, allergic sinusitis, or hay fever	1.5	(0.8-2.8)	2.8	(1.0-7.8)	1.8	(1.1-3.1)
Savica et al., 2009 ^b	Anemia	Diagnosis of anemia or low hemoglobin	1.5	(0.9-2.6)	2.9	(1.5-5.8)	2.0	(1.3-3.1)
Family history risk factors ^d								
Rocca et al., 2004	Parkinsonism ^e	Defined using specified criteria or reported at interview	1.4	(0.6-3.0)	0.9	(0.4-2.1)	1.1	(0.6-2.0)
Rocca et al., 2007	Essential Tremor ^e	Defined using specified criteria or reported at interview	1.1	(0.5-2.4)	1.5	(0.6-3.8)	1.2	(0.7-2.2)
Rocca et al., 2007	Dementia	Defined by cognitive testing or reported by an informant	1.6	(0.9-2.8)	1.0	(0.5-2.1)	1.3	(0.8-2.1)
Arabia et al., 2007	Psychiatric disorders	Defined using specified criteria or reported at interview	1.3	(0.7-2.5)	2.5	(1.2-5.6)	1.7	(1.1-2.8)

OR=odds ratio CI=confidence interval PD=Parkinson's disease

^aDetails about data collection and definition of each risk or protective factor are provided in the corresponding published paper.

^bRisk or protective factors present in the history of cases and controls were obtained by abstracting the complete set of medical records in a records-linkage system.

^cAlthough cigarette smoking was not significantly associated with PD in our sample, it was considered in the analyses because of the consistent findings in other studies.

^dFamily history risk factors were obtained through an extensive study of the familial aggregation of neurological diseases in first-degree relatives of PD cases and controls. However, for this study we collapsed the full pedigree information for each subject into a dichotomous variable, family history positive or negative. The results from case-control analyses shown here (OR and 95% CI) are unpublished. Because some subjects had missing family information, the matching was ignored and the models included age (in quartiles) and sex.

^eThe hazard ratios for familial aggregation of parkinsonism or of essential tremor did not reach statistical significance for the overall sample in the original publications; however, the hazard ratios were statistically significant in the stratum of younger onset PD (< 66 years).