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Original Contribution

Peripheral Inflammatory Biomarkers and Risk of Parkinson's Disease

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Experimental and postmortem evidence indicates a role of neuroinflammation in the pathogenesis of Parkinson's disease. The authors prospectively examined whether plasma concentrations of inflammatory biomarkers assessed before Parkinson's disease diagnosis were predictive of future risk of the disease in a nested case-control study in the United States (1993–2002), including 84 incident cases and 165 matched controls. Blood was collected from patients on average 4.3 years before the diagnosis. After adjustment for potential confounders, higher level of interleukin-6 was associated with a greater risk of Parkinson's disease. Compared with the lowest quintile, the odds ratios were 1.5 for the second, 1.6 for the third, 2.7 for the fourth, and 3.4 for the fifth quintiles (p for trend = 0.03). In contrast, concentrations of other inflammatory biomarkers including C-reactive protein, fibrinogen, and tumor necrosis factor-α receptors were not related to the risk. These data suggest that men with high plasma concentrations of interleukin-6 have an increased risk of developing Parkinson's disease. However, this finding should be interpreted with caution because of the small sample size and the lack of associations with other biomarkers of inflammation.

biological markers; C-reactive protein; inflammation; interleukin-6; odds ratio; Parkinson disease; tumor necrosis factor-α

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

Microglia-mediated neuroinflammation has been hypothesized to play an important role in the pathogenesis of Parkinson's disease, primarily based on findings from postmortem studies and animal experiments (1, 2). Consistently, concentrations of proinflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, and tumor necrosis factor (TNF)-α were elevated in the brain and cerebral spinal fluid of Parkinson's disease patients (3). Two small studies further showed plasma elevations of some of these cytokines when comparing Parkinson's disease patients with controls (4, 5). However, these studies involved prevalent cases and provided little information on whether prediagnostic levels of inflammatory biomarkers are predictive of future risk of Parkinson's disease. Therefore, by taking advantage of the prospective Health Professionals Follow-up Study, we conducted a nested case-control investigation to examine whether peripheral elevations in inflammatory biomarkers assessed years before disease diagnoses were associated with greater risk of Parkinson's disease.

MATERIALS AND METHODS

Study population

The Health Professionals Follow-up Study includes 51,529 male health professionals in the United States who

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have been closely followed via biennial surveys since 1986 to ascertain their dietary and lifestyle habits and the occurrence of major chronic diseases. From April 1993 through August 1995, all active participants in the cohort were requested to donate a blood sample; the 18,018 (35 percent) men who provided blood samples constituted the base population for the current research. Participants who donated samples were somewhat younger but were otherwise similar to those who did not (6). After blood collection, 84 incident Parkinson's disease cases were identified according to a standardized procedure (7). For each case, two controls were randomly selected from men who did not report a diagnosis of Parkinson's disease and were still alive at the time of the case's diagnosis, matching on year of birth, race (White/other), fasting status at blood draw (>8 hours vs. less or unknown), time of day of the blood draw in 2-hour intervals, and month and year of blood draw.

Case ascertainment

Self-reported Parkinson's disease diagnoses were first identified via our regular biennial surveys from 1988 through 2002. After obtaining permissions, we asked participants' treating neurologists (or internists if neurologists did not respond) to complete a questionnaire to confirm the diagnosis and to provide their judgment on the certainty of diagnosis or to send a copy of the medical record. A case was confirmed if the diagnosis was considered definite or probable by the treating neurologist or if the medical record included either a final diagnosis of Parkinson's disease made by a neurologist or evidence at a neurologic examination of at least two of the three cardinal signs (rest tremor, rigidity, bradykinesia) in the absence of features suggesting other diagnoses. Medical records were reviewed by our movement disorder specialist, blind to exposure status. Overall in the cohort, the diagnosis was confirmed by the treating neurologists in 82.3 percent of the cases, by reviewing medical records in 6.4 percent, and by the treating internist in the remaining 11.3 percent. Hughes et al. (8) recently reported that accuracy of clinical Parkinson's disease diagnosis by neurologists had improved in the 1990s to 90 percent.

Assessment of exposure

Blood samples were returned to our laboratory via overnight courier, more than 95 percent within a 24-hour interval. Upon arrival, blood samples were centrifuged and blood components were aliquotted into cryotubes and stored in the vapor phase of liquid nitrogen freezers. Plasma samples from Parkinson's disease cases and controls were sent to the laboratory in random order, and all assays were conducted without knowledge of case/control status. Plasma concentrations of high-sensitivity C-reactive protein, IL-6, soluble TNF-α receptor types 1 and 2, and fibrinogen were determined by sensitive analytic methods that have been described previously (9, 10). In addition, we also measured plasma concentrations of creatinine and uric acid according to established protocols (10).

Statistical analyses

We first calculated the Spearman correlation coefficients for controls to examine the interrelations among these biomarkers. In the primary analyses, we categorized plasma concentrations of inflammatory biomarkers into quintiles according to their distributions among controls. We used conditional logistic regression to calculate the odds ratios, which directly estimates the relative risk because the risk-set sampling strategy was used to select controls. The odds ratios were first adjusted for age and pack-years of smoking (never smokers; pack-years: 0–14, 15–29, 30–49, and $\geq$50) and then further for caffeine intake (in quintiles) and plasma levels of uric acid (continuous) and creatinine (continuous). We included uric acid in the model because in both this (11) and other prospective studies (12, 13), higher uric acid concentration was linked to a lower risk of Parkinson's disease. Creatinine was used as an indicator of renal function, which has important impacts on plasma levels of some inflammatory biomarkers (14).

In addition, we also considered a few other potential confounders, adjustment of which did not materially change the results, however. These covariates included physical activity, body mass index, use of non-aspirin nonsteroidal anti-inflammatory drugs, medical history of physician-diagnosed diabetes or hypertension, and dairy intake. Information on most questionnaire covariates was obtained from the 1992 follow-up survey because it was the latest before blood collection. For caffeine intake and other dietary data, we used the 1990 survey because diet was assessed every 4 years. For body mass index and physical activity, we used the 1986 data because Parkinson's disease patients tend to lose weight and decrease their physical exercise about 4 years before the diagnosis (15, 16).

To test the robustness of our results and to reduce the effect of disease progress around the time of diagnosis on plasma levels of inflammatory biomarkers, we conducted a lag analysis by excluding the first 4 years of follow-up. Further lag analysis was impossible because of the small sample size. All statistical tests were two sided, with $\alpha = 0.05$.

RESULTS

The average age of Parkinson's disease patients at diagnosis was 71.5 years (range, 55–85). The average time between blood collection and Parkinson's disease diagnosis was 4.3 years, with 50 percent of the cases ($n = 42$) being diagnosed more than 4 years after blood collection. As expected, cases were less likely than controls to smoke cigarettes or drink coffee (table 1), but they were similar to controls regarding other population characteristics. Among these inflammatory biomarkers, TNF-α receptor type 1 and TNF-α receptor type 2 were highly correlated (table 2); the correlation coefficients between other pairs of inflammatory biomarkers were moderate, ranging from 0.14 to 0.48. Furthermore, plasma concentrations of C-reactive protein, fibrinogen, and IL-6 were also moderately correlated with that of uric acid; in contrast, TNF-α receptor type 1 and

TABLE 1. Baseline population characteristics of Parkinson's disease cases and controls*,†, United States, 1993–2002

	Cases ($n = 84$)	Controls ($n = 165$)
Age at blood donation (years)	67.2 (7.6)	67.2 (7.5)
Pack-years of smoking (no.)	11.0 (18.1)	14.2 (18.3)
Ever smoker	46.2	57.3
Caffeine intake (mg/day)	166 (171)	237 (228)
Physical activity (MET‡ hours/week)	18.2 (23.8)	20.4 (22.7)
Body mass index (kg/m^2)	25.4 (3.2)	25.6 (3.5)
Nonaspirin nonsteroidal antiinflammatory drug use	11.0	10.4
Dairy consumption (servings/day)	1.8 (1.1)	2.0 (1.6)
History of diabetes	3.8	3.8
History of hypertension	30.0	32.1
Uric acid (mg/dl)	5.7 (1.1)	6.2 (1.4)
Plasma creatinine (mg/dl)	1.0 (0.2)	1.1 (0.2)
Inflammatory markers		
High-sensitivity C-reactive protein (mg/liter)	1.03 (0.58–2.03)	0.98 (0.54–2.06)
Interleukin-6 (pg/ml)	1.37 (0.87–2.26)	1.24 (0.77–1.99)
Fibrinogen (mg/dl)	405 (63.6)	404 (69.9)
Tumor necrosis factor-α receptor type 1 (pg/ml)	1,407 (409)	1,448 (416)
Tumor necrosis factor-α receptor type 2 (pg/ml)	2,436 (637)	2,508 (719)

* Means (standard deviations) are presented for continuous variables with the exception of C-reactive protein and interleukin-6 (which are presented as medians (interquartile ranges) because of highly skewed distributions); proportions are presented for categorical variables; missing values were not taken into account.

† For most questionnaire variables, data from the 1992 survey were used; for caffeine intake and other dietary variables, data from the 1990 survey were used; for body mass index and physical activity, data from the 1986 survey were used.

‡ MET, metabolic equivalent task.

TNF-α receptor type 2 concentrations were correlated with creatinine concentration but not with plasma level of uric acid.

Plasma concentration of IL-6 tended to be positively associated with Parkinson's disease risk, and the association was stronger in the multivariate model (table 3): the risk increment between extreme quintiles was more than threefold, with a significant linear trend. Further adjusting for other potential confounders either individually or simultaneously generated similar results; the odds ratios between extreme quintiles of IL-6 were 3.4 (p for trend = 0.03) after further adjusting for physical activity, body mass index, or diabetes and hypertension; 3.2 (p for trend = 0.04) after adjusting for nonsteroidal antiinflammatory drug use; 3.3 (p for trend = 0.05) after adjusting for dairy intake; and 3.2 (p for trend = 0.04) with all potential confounders in the same model. The association remained when we included only neurologist-diagnosed cases; the odds ratios for increasing IL-6 quintiles were 1.0, 1.6, 2.0, 2.4, and 3.7 (95 percent confidence interval: 1.0, 4.6; p for trend = 0.06), respectively. These risk increments also persisted in the 4-year lag analysis, although the statistical tests were no longer significant because the sample size diminished: the corresponding odds ratios were 1.0, 2.3, 6.4, 4.5, and 5.5 (95 percent confidence interval: 0.8, 40.5; p for trend = 0.3), respectively. Concentrations of other inflammatory biomarkers were not related to the risk of Parkinson's disease (table 3).

DISCUSSION

In this nested case-control study, elevated plasma IL-6 concentration was prospectively associated with an increased risk of developing Parkinson's disease. The risk elevation was independent of known Parkinson's disease risk factors and persisted after the first several years of follow-up were excluded. Because blood was collected on average 4 years before disease diagnosis, the increment of peripheral IL-6 may indicate a chronic inflammatory process years before Parkinson's disease diagnosis. In contrast to IL-6, although slightly higher risk was also observed for higher concentrations of some other biomarkers, none of them was statistically significant.

TABLE 2. Age-adjusted Spearman correlation coefficients for baseline biomarkers among controls, United States, 1993–2002

	Fibrinogen	IL†-6	TNF-R1†	TNF-R2†	Uric acid	Creatinine
hs-CRP†	0.46****	0.48****	0.24**	0.30****	0.34****	0.05
Fibrinogen		0.26***	0.14	0.23**	0.20*	0.11
IL-6			0.22**	0.19*	0.20*	0.01
TNF-R1				0.72****	0.12	0.40****
TNF-R2					0.14	0.36****
Uric acid						0.19*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$.

† IL, interleukin; TNF-R1, tumor necrosis factor-α receptor type 1; TNF-R2, tumor necrosis factor-α receptor type 2; hs-CRP, high-sensitivity C-reactive protein.

TABLE 3. Odds ratios of Parkinson's disease according to inflammatory biomarker concentration, United States, 1993–2002

	Quintile of plasma concentration									
	1	2		3		4		5		*p* trend
	OR*	OR	95% CI*	OR	95% CI	OR	95% CI	OR	95% CI	
hs-CRP* (mg/liter)	≤0.45	0.46–0.75		0.76–1.30		1.31–2.44		≥2.45		
No. of cases	13	21		15		18		17		
Age and smoking adjusted	1.0 (ref*)	1.5	0.7, 3.6	1.1	0.4, 2.7	1.4	0.6, 3.1	1.1	0.4, 2.7	0.9
Multivariate adjusted†	1.0 (ref)	1.5	0.6, 3.7	1.3	0.5, 3.7	1.9	0.8, 4.9	1.5	0.5, 4.1	0.6
Fibrinogen (mg/dl)	≤346	346–375		376–415		416–462		≥463		
No. of cases	16	10		25		18		15		
Age and smoking adjusted	1.0 (ref)	0.6	0.2, 1.6	1.5	0.6, 3.6	1.2	0.5, 2.8	0.9	0.3, 2.5	0.95
Multivariate adjusted†	1.0 (ref)	0.7	0.2, 2.0	2.0	0.8, 5.3	1.6	0.6, 4.5	1.2	0.4, 3.7	0.6
IL*-6 (pg/ml)	≤0.69	0.70–1.08		1.08–1.48		1.49–2.17		≥2.17		
No. of cases	13	15		15		17		24		
Age and smoking adjusted	1.0 (ref)	1.1	0.4, 2.9	1.1	0.4, 2.8	1.6	0.6, 4.4	2.0	0.7, 5.2	0.1
Multivariate adjusted†	1.0 (ref)	1.5	0.5, 4.5	1.6	0.5, 4.8	2.7	0.8, 9.1	3.4	1.1, 10.5	0.03
TNF-R1* (pg/ml)	≤1,112	1,113–1,277		1,278–1,479		1,480–1,677		≥1,678		
No. of cases	19	19		15		12		19		
Age and smoking adjusted	1.0 (ref)	1.0	0.4, 2.4	0.8	0.3, 2.1	0.5	0.2, 1.5	1.0	0.4, 2.5	0.9
Multivariate adjusted†	1.0 (ref)	0.8	0.3, 2.1	0.8	0.3, 2.2	0.5	0.2, 1.6	1.3	0.4, 3.7	0.6
TNF-R2* (pg/ml)	≤1,959	1,960–2,233		2,233–2,555		2,556–2,890		≥2,891		
No. of cases	16	22		18		8		20		
Age and smoking adjusted	1.0 (ref)	1.8	0.7, 4.8	1.1	0.4, 2.7	0.6	0.2, 1.7	1.3	0.5, 3.7	0.95
Multivariate adjusted†	1.0 (ref)	2.3	0.8, 6.6	1.5	0.6, 3.9	0.7	0.2, 2.3	2.7	0.8, 8.8	0.3

* OR, odds ratio; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; ref, referent; IL, interleukin; TNF-R1, tumor necrosis factor-α receptor type 1; TNF-R2, tumor necrosis factor-α receptor type 2.

† Adjusted for age, smoking, caffeine intake, uric acid level, and creatinine level.

IL-6 has both proinflammatory and antiinflammatory activities. In the central nervous system, it is expressed on specific neurons, astrocytes, and microglia and could be induced by both proinflammatory cytokines such as IL-β and TNF-α and, in the cases of glia, viral and bacterial pathogens such as lipopolysaccharide (17, 18). Although elevated levels of IL-6 in the brain have been considered evidence of neuroinflammation, its specific roles in Parkinson's disease pathogenesis are not clear. In animal models, both protective and detrimental effects of IL-6 toward the dopaminergic system have been reported. Goodwill et al. (19) showed that IL-6 knockout prevented mice from polychlorinated biphenyls–induced striatal dopaminergic dysfunctions; on the other hand, a neuroprotective effect of IL-6 was observed in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced parkinsonian mice (20).

The lack of association with TNF-α receptors requires a cautious interpretation because, in cross-sectional studies, TNF-α has been reported to be elevated in brains (3), cerebrospinal fluid (3, 21), and blood (5) of Parkinson's disease patients. On the other hand, single or double knockout of TNF-α receptors did not prevent the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in animal experiments (22). Furthermore, we used soluble TNF-α receptors as surrogates for circulating TNF-α in the analysis because circulating TNF-α has a very short half-life; the value of this approach in investigating TNF-α and disease association is uncertain, however (9). Therefore, the lack of a positive finding regarding TNF-α and Parkinson's disease may be a result of measurement errors. High-sensitivity C-reactive protein, an important risk factor for cardiovascular disease (23) and possibly dementia (24), has not been implicated in any Parkinson's disease research. In addition, the peripheral C-reactive protein concentration is much higher than that in the central nervous system (25); therefore, even a marked C-reactive protein elevation in the central nervous system may not be adequate to increase its circulation level. The lack of a systemic elevation of C-reactive protein may indirectly suggest that the moderate elevation in IL-6 we observed in blood may originate from the brain and reflect a local rather than chronic systemic inflammatory process. Nevertheless, the finding that IL-6 but not other inflammatory biomarkers (particularly TNF-α) elevates in early Parkinson's disease pathogenesis was not hypothesized a priori. Therefore, the relevance of these findings to Parkinson's disease pathogenesis should be further evaluated.

While our result on IL-6 is consistent with the notion that neuroinflammation may start at an early stage of Parkinson's disease, it does not prove it. First, we measured only the peripheral concentration of IL-6, which might not reflect

changes in the central nervous system. Furthermore, the elevation in IL-6 in future Parkinson's disease patients could simply be a compensatory response to the neurodegeneration process (21). Finally, the lack of associations with TNF-α receptors and other inflammatory biomarkers prevented us from drawing a solid conclusion about inflammation and Parkinson's disease. However, the hypothesis that neuroinflammation contributes to Parkinson's disease pathogenesis would be consistent with previous epidemiologic findings that nonsteroidal antiinflammatory drug use was associated with a lower Parkinson's disease risk (26, 27). Further support for this hypothesis includes marked and ongoing gliosis around dopaminergic neurons in monkey (28) and human parkinsonian sufferers (29) years after exposures to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, suggesting a chronic and self-perpetuated neuroinflammation process in parkinsonism.

Being the first known prospective investigation on peripheral inflammatory biomarkers and Parkinson's disease, our analyses should be considered exploratory. We could not exclude the possibility of chance or unmeasured confounding as alternative explanations for our findings. Furthermore, the small sample size limited our statistical power in the analyses, and single point measurements of plasma biomarkers of inflammation are subject to day-to-day variations and did not enable us to examine potential changes in biomarkers associated with the disease process. Nevertheless, our data provide preliminary evidence of preclinical chronic inflammation among Parkinson's disease patients. This finding needs to be confirmed by larger prospective studies with more comprehensive assessments of proinflammatory cytokines and a longer follow-up period.

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Conflict of interest: none declared.

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