Original Contribution

Plasma Urate and Risk of Parkinson’s Disease

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Oxidative stress contributes to dopaminergic neuron degeneration in Parkinson’s disease. Urate, a potent antioxidant, could be neuroprotective. To determine whether higher plasma concentrations of urate predict a reduced risk of Parkinson’s disease, the authors conducted a nested case-control study among participants in the Health Professionals Follow-up Study, a cohort comprising over 18,000 men who provided blood samples in 1993–1995. Eighty-four incident cases of Parkinson’s disease were diagnosed through 2000, and each was randomly matched to two controls by year of birth, race, and time of blood collection. Rate ratios of Parkinson’s disease according to quartile of uricemia were estimated by use of conditional logistic regression. The mean urate concentration was 5.7 mg/dl among cases and 6.1 mg/dl among controls (p = 0.01). After adjustment for age, smoking, and caffeine, the rate ratio of Parkinson’s disease for the highest quartile of uricemia compared with the lowest was 0.43 (95% confidence interval: 0.18, 1.02; p_trend = 0.017). This association was stronger in analyses excluding cases diagnosed within 4 years (median) from blood collection (rate ratio = 0.17, 95% confidence interval: 0.04, 0.69; p_trend = 0.010). These results suggest that high plasma urate concentrations may decrease the risk of Parkinson’s disease, and they raise the possibility that interventions to increase plasma urate may reduce the risk and delay the progression of Parkinson’s disease.

Parkinson disease; prospective studies; uric acid

Abbreviation: CI, confidence interval.

Plasma urate concentrations are low in most mammals, because of urate’s degradation by uricase. Several mutations in the gene encoding uricase during evolution, however, have resulted in the complete loss of a functional enzyme in apes and humans and a severalfold increase in uricemia. It has been proposed that this loss may reflect a beneficial effect of urate against aging, related to its ability to prevent the oxidative damage caused by reactive nitrogen and oxygen species (1). Because oxidative stress appears to play a key role in the progressive loss of dopaminergic neurons in the substantia nigra that characterizes Parkinson’s disease (2), urate could be an important determinant of disease susceptibility. The association between urate and risk of Parkinson’s disease has been investigated in only two previous prospective studies; in both, there was a trend suggesting that individuals with high serum urate have a lower risk of Parkinson’s disease, but these associations were either not significant or only marginally significant (3, 4), and whether urate predicts Parkinson’s disease risk remains uncertain. We have therefore conducted a nested case-control study among participants in the Health Professionals Follow-up Study to examine the a priori hypothesis that high plasma

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levels of urate predict a reduced risk of developing Parkinson’s disease.

**MATERIALS AND METHODS**

**Study population**

The Health Professionals Follow-up Study was established in 1986, when 51,529 male health professionals (dentists, optometrists, pharmacists, osteopaths, podiatrists, and veterinarians), aged 40–75 years, responded to a mailed questionnaire that included a comprehensive diet survey, in addition to questions on disease history and lifestyle (5). Participants are mostly White and of European ancestry. Follow-up questionnaires are mailed to participants every 2 years to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred. From April 1993 through August 1995, blood samples were collected from 18,018 participants in the Health Professionals Follow-up Study cohort. Participants were followed for incidence of Parkinson’s disease until the return of the 2002 questionnaire. Those with a history of cancer or Parkinson’s disease before blood collection were excluded from the study. For each confirmed case of Parkinson’s disease, we randomly selected two controls among men who had no report of Parkinson’s disease and were alive at the time of the Parkinson’s disease diagnosis of their matched case. The controls were matched 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. The research herein was approved by the human subjects committees of the Brigham and Women’s Hospital and the Harvard School of Public Health.

**Case ascertainment**

Ascertainment of the Parkinson’s disease cases in this cohort has been described previously (6). In brief, after obtaining permission, we asked the treating neurologist of cohort participants who reported a new diagnosis of Parkinson’s disease (or internist if the neurologist did not respond) to complete a questionnaire to confirm the diagnosis of Parkinson’s disease and the certainty of the diagnosis or to send a copy of the medical record. A case was confirmed if a diagnosis of Parkinson’s disease was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of Parkinson’s disease made by a neurologist or evidence at a neurologic assessment of at least two of the four cardinal signs of Parkinson’s disease (with one being rest tremor or bradykinesia), a progressive course, and the absence of unresponsiveness to levodopa (L-dopa) or other features suggesting an alternative diagnosis. The review of medical records was conducted by the investigators, blind to the exposure status. Overall, the diagnosis was confirmed by the treating neurologist in 82 percent of the cases, by review of the medical records in 6 percent, and the rest by the treating internist without further support. Because the diagnosis of idiopathic Parkinson’s disease remains essentially clinical, the certainty of diagnosis was left to the judgment of the clinician, which has been found to be highly reliable (7). Deaths in the cohort were reported by family members, coworkers, or postal authorities, or they were identified by searching the National Death Index. If Parkinson’s disease was listed as a cause of death on the death certificate, we requested permission from the family to contact the treating neurologist or physician and followed the same procedure as for the nonfatal cases.

**Assessment of exposure**

The blood samples were returned to our laboratory via overnight courier; over 95 percent of the samples arrived within 24 hours of being drawn. Upon arrival in our laboratory, the blood samples were centrifuged, and blood components were aliquoted into cryotubes and stored in the vapor phase of liquid nitrogen freezers. The concentration of urate was determined by a colorimetric enzyme assay on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, Indiana). The day-to-day variabilities of the assay at concentrations of 4.86, 7.20, and 9.39 mg/dl are 1.3, 1.7, and 1.6 percent, respectively. Because the determination of serum urate was conducted specifically for this study and not as part of a blood chemistry panel, results of other routine chemistry tests are not available in these samples.

**Statistical analyses**

To account for the matched design of the study, we used conditional logistic regression to estimate odds ratios of Parkinson’s disease according to plasma levels of urate, and their 95 percent confidence intervals. Under the design of this study, the odds ratios from conditional logistic regression estimate the corresponding rate ratios. For this reason, we have used the latter term throughout the paper. In the main analyses, we categorized plasma levels of urate into quartiles defined according to the distribution of urate among controls. Tests for trend were conducted by including urate as a continuous variable in the conditional logistic regression models. Comparison of means between cases and controls was done by use of random effects models to account for correlation within matched sets. Data on additional covariates considered in analyses were taken from responses to the 1992 questionnaire—the most recent survey prior to the period of blood donation—except for dietary data (including vitamin use), which were derived from a semiquantitative food frequency questionnaire administered in 1990 (6) because dietary data were not collected in 1992, and data on physical activity, which were from the 1986 questionnaire. These covariates included pack-years of smoking; caffeine intake (mg/day); alcohol intake (g/day); body mass index (kg/m²); physical activity (metabolic equivalents/week); dairy, meat, and fish consumption (servings/day); regular use of aspirin or other nonsteroidal anti-inflammatory drug use (≥2 per week vs. less); use of thiazide or other diuretics; and history of hypertension or gout. Indicator variables were created for covariates with missing data. In regression models, alcohol was split into categories based on grams per day (0, 1–9, 10–19, 20–29,

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RESULTS

We identified 84 incident cases of Parkinson’s disease diagnosed after the time of blood collection. The mean age at Parkinson’s disease diagnosis was 71.5 years (range: 55–85 years). The mean plasma urate concentration was 5.7 mg/dl (339 μmol/liter) among cases and 6.1 mg/dl (363 μmol/liter) among the 165 matched controls (p = 0.0097). Table 1 shows the distribution of covariates among controls by quartile of urate concentration.

In analyses adjusted for age, pack-years of smoking, and quintiles of caffeine intake, the rate ratio for Parkinson’s disease decreased with increasing urate quartile (figure 1A). The rate ratio for the highest quartile compared with the lowest was 0.43 (95 percent confidence interval (CI): 0.18, 0.91).
There was also a significant dose-response relation when urate was analyzed as a continuous variable. The rate ratio for Parkinson’s disease per unit (mg/dl) increase in urate concentration was 0.76 (95 percent CI: 0.61, 0.95; \( p = 0.017 \)). In order to reduce the possibility that unrecognized Parkinson’s disease could affect urate concentrations, we also did analyses restricted to cases whose blood was drawn more than 4 years before their Parkinson’s disease diagnosis and their matched controls. The numbers of cases and controls in each quartile of urate concentration are shown at the bottom of each graph.

1.02). There was also a significant dose-response relation when urate was analyzed as a continuous variable. The rate ratio for Parkinson’s disease per unit (mg/dl) increase in urate concentration was 0.76 (95 percent CI: 0.61, 0.95; \( p = 0.017 \)). In order to reduce the possibility that unrecognized Parkinson’s disease could affect urate concentrations, we also did analyses restricted to cases whose blood was drawn more than 4 years before their Parkinson’s disease diagnosis and their matched controls. The association was stronger in these analyses (figure 1B). The rate ratio for the highest quartile compared with the lowest was 0.17 (95 percent CI: 0.04, 0.69; \( p = 0.013 \)), and the rate ratio for Parkinson’s disease per unit (mg/dl) increase in urate concentration was 0.62 (95 percent CI: 0.43, 0.89; \( p = 0.010 \)). Neither history of hypertension nor use of thiazide diuretics was significantly associated with risk of Parkinson’s disease, and the association between plasma urate and Parkinson’s disease risk was virtually unchanged after adjustment for these variables. Further, the results were not materially affected when the analyses were adjusted additionally for alcohol intake, quintiles of physical activity and body mass index, quintiles of dairy consumption, quintiles of total protein intake, and regular use of nonsteroidal anti-inflammatory drug use (yes/no) either individually or simultaneously.

A similar pattern of results was seen when analyses were run on the basis of specific cutoff points of urate concentration. Considering urate concentrations of < 5, 5–<5.5, 5.5–<6, 6–<6.5, 6.5–<7, and ≥7 (all in mg/dl), the numbers of cases/controls in each of those ranges, respectively, were 22/27, 10/22, 19/30, 11/23, 10/20, and 12/43. The rate ratio for Parkinson’s disease for those with urate greater than or equal to 7 mg/dl compared with those with urate less than 5 mg/dl was 0.38 (95 percent CI: 0.15, 0.96) adjusting for age, pack-years of smoking, and caffeine. In the analysis restricted to cases whose blood was drawn more than 4 years prior to the diagnosis of Parkinson’s disease, the numbers of cases/controls were 10/10, 8/11, 8/14, 7/14, 5/12, and 4/23 in the respective categories. The rate ratio for Parkinson’s disease for those with urate greater than or equal to 7 mg/dl compared with those having urate less than 5 mg/dl was 0.15 (95 percent CI: 0.03, 0.63) adjusting for age, pack-years of smoking, and caffeine.

We also explored the possibility of interactions between urate concentration and other covariates. No significant interactions were found with age at blood collection, pack-years of smoking, caffeine, or alcohol.

In the meta-analysis of the results of the present study and those of the two previous prospective investigations, the pooled rate ratio of Parkinson’s disease associated with a standard deviation increase in urate (1.32 mg/dl) was 0.80 (\( p = 0.000074 \)) (figure 2).

**DISCUSSION**

In this large, prospective investigation, we found that men in the top quartile of plasma urate concentration had a 55 percent lower rate of Parkinson’s disease than did men in the bottom quartile. The decrease in Parkinson’s disease rate among men with high levels of urate was stronger among men with blood collected at least 4 years before the diagnosis of Parkinson’s disease, suggesting that the low level of plasma urate among individuals with Parkinson’s disease precedes the onset of neurologic symptoms and is thus unlikely to be a consequence of changes in diet, behavior, or medical treatment early in the course of the disease. Further, this inverse association was independent from age, smoking, caffeine consumption, and other aspects of lifestyle that have been related to both Parkinson’s disease and uricemia.

The difference in plasma urate concentration between cases and controls in our study is unlikely to be artifactual, because both groups were drawn from the same population and because their plasma samples were collected at the same time, processed and stored in the same manner, and sent in random order and without disease status identification for laboratory analyses. A limitation of the present study is that we could not physically examine the participants, and therefore we relied on diagnoses of Parkinson’s disease made by the treating neurologists or confirmed by review of the
with serum urate above the median as compared with those of Parkinson’s disease were 40 percent lower among men followed for 30 years, the age- and smoking-adjusted rates of Parkinson’s disease. Consistently with these previous studies and that presented here is impressive, and the pooled results provide compelling evidence of a decreasing rate of Parkinson’s disease for higher levels of urate.

Because of its observational design, the results of the present and previous investigations cannot establish whether high levels of urate are causally related to the rate of Parkinson’s disease, or whether uricemia and a low rate of Parkinson’s disease share an unknown common cause. A preventive effect of uricemia, however, would be consistent with the strong evidence for a role of oxidative stress in the progressive degeneration of dopaminergic neurons in individuals with Parkinson’s disease (2, 11). The oxidative metabolism of dopamine can produce hydrogen peroxide and other reactive oxygen species, as well as conditions favorable to oxidative stress, including increased iron (12, 13) and decreased glutathione, and signs of oxidative damage to lipids, proteins, and DNA have been observed in postmortem Parkinson’s disease brains (11). Urate is present in plasma at the high concentrations maintained by active kidney reabsorption (1, 14). Urate in physiologic concentrations is as effective as ascorbate in preventing lipid peroxidation initiated in vitro by hydrogen peroxide (1); stabilizes ascorbate (15), possibly by forming complexes with iron ions (16); and scavenges nitrogen radicals (17, 18), which have a critical role in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurotoxicity, an animal model of Parkinson’s disease (19, 20). Further, administration of urate reduced the homocysteine-induced exacerbation of the oxidative stress and mitochondrial dysfunction in human dopaminergic cells exposed to the pesticides rotenone or to iron ions (21).

Although the cerebrospinal fluid urate concentration is only about 7 percent that of plasma, there is a strong correlation between plasma and cerebrospinal fluid urate (22), and, in spite of being present at low concentrations, urate could still be important in the brain because of its antioxidant effects (23) or its ability to stabilize ascorbate. It is also possible that a localized increase in the blood-brain barrier permeability precedes the clinical onset of Parkinson’s disease. Changes in blood vessels in the substantia nigra of Parkinson’s disease patients have been described (24), and the results of a recent study provide preliminary evidence of a blood-brain barrier dysfunction (25). Urate seems to prevent the increase in permeability of the blood-brain barrier observed in inflammatory diseases of the central nervous system, such as Borna disease virus encephalitis (26) or experimental allergic encephalomyelitis, an animal model of multiple sclerosis (27–30). Consistently with the results in experimental allergic encephalomyelitis, low urate has been associated with optic neuritis (31) and multiple sclerosis (32–34).
The hypothesis that uricemia could effectively reduce the susceptibility to Parkinson’s disease has potentially important therapeutic implications, because plasma levels of urate can be increased by inosine, a urate precursor sold over the counter as a nutritional supplement and athletic performance enhancer (35), which is now being tested in a randomized trial for multiple sclerosis treatment (36). A primary prevention trial for Parkinson’s disease would be unfeasible, because elevated levels of urate are an important risk factor for cardiovascular diseases and overall mortality. In the Honolulu Heart Program cohort itself, men in the top quartile of serum urate concentration had a reduced rate of Parkinson’s disease but a 20 percent increased total mortality rate. Whether uricemia itself is harmful or whether it is a marker of an underlying systemic stress remains to be established, but, if the harm is real, any putative beneficial effect of increasing plasma urate concentration on risk of Parkinson’s disease would be offset by increased cardiovascular morbidity and mortality. A more cogent question, therefore, is whether increasing the plasma urate concentration could decelerate the progression of neurodegeneration among individuals with Parkinson’s disease, for whom the benefits of neuroprotection could possibly outweigh the potential adverse effects. The recent findings of a slower rate of Parkinson’s disease progression among individuals with higher serum urate (37) or cerebrospinal fluid urate (38) concentrations support this possibility.

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Conflict of interest: none declared.

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