Stroke and Parkinson's Disease

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Background and Purpose: We sought to determine whether the recently reported decreased incidence of stroke and atherosclerotic disease in a university hospital–based Parkinson's disease patient population would be demonstrated in our patient population.

Methods: We performed a retrospective case–control review of the last 119 Parkinson's disease patients discharged from the Middleton Veterans Affairs Hospital Neurology Service to study the incidence of ischemic stroke, myocardial ischemia, tobacco use, and other stroke risk factors. Controls were age and sex matched and were randomly taken from 238 non–Parkinson's disease discharges in which stroke or myocardial infarction was not the reason for hospitalization.

Results: The cumulative incidences of ischemic stroke, hypertension, and diabetes mellitus were not significantly different between groups. Myocardial infarction, coronary artery disease, tobacco use, atrial fibrillation, cancer, and ethanol abuse were significantly more prevalent in the controls, whereas dementia and congestive heart failure were the only variables studied that were more prevalent in the Parkinson's disease patients.

Conclusions: Our study failed to demonstrate that Parkinson's disease patients from a Veteran population were protected from ischemic stroke. (Stroke 1992;23:839–842)

Key Words • cerebral ischemia • Parkinson disease • risk factors

Ischemic stroke and Parkinson's disease (PD) are common disorders in our aging population. Atherosclerosis has been suggested as a possible cause of PD by some authors and dismissed as a possible cause by others.1 Degenerative cerebrovascular disease and PD afflict similar age groups, and some manifestations of cerebral atherosclerosis may be clinically difficult to distinguish from those of PD.

In reference to the recent work of Struck et al,2 we report a case–control retrospective study of the incidence of ischemic stroke in a Veterans Affairs (VA) hospital patient population. Some previous studies have found a higher incidence of ischemic stroke in PD patients compared with control subjects,3 some a lower incidence,2,4 and some a similar incidence.5,6 In the most recent studies, the decreased incidence of ischemic stroke in PD patients appears to be related to less-severe generalized atherosclerosis, possibly due to their lower incidence of tobacco use.1,2 In addition, the dopamine depletion in PD patients is considered to provide “protective” benefit from developing ischemic stroke.1,7,8 Thus, we report an investigation of cerebrovascular status and risk factors in patients with and without PD discharged from our facility.

Subjects and Methods

We performed a retrospective case–control review of the last 119 PD patients discharged from the Middleton VA Hospital Neurology Service. Data were compiled to make a direct comparison with those in the recent retrospective study at the University of Iowa Hospitals and Clinics.2 The study continued from 1982 through 1990. Patients with PD included those with a presumptive etiology of "idiopathic," and all diagnoses were reconfirmed by either the attending neurologist or a review of subsequent outpatient follow-up records. All patients were male veterans of mean age 68.5 (range, 49–94) years. The mean duration of illness was 7.3 (range, 1–40) years when discharged. Severity of PD was rated, according to the Hoehn and Yahr classification,3 from stage I to stage V. Anti-PD agents were recorded by drug type at discharge.

The control population was randomly chosen from all non-PD discharges from the Middleton VA Hospital Medical Service over the same time period. Two control subjects were chosen for each PD patient, matching for male sex and precisely matching for age. The 238 control subjects did not have stroke or myocardial infarction as a primary reason for admission and did not suffer stroke as a complication of being hospitalized. Mean age and age range of the control group were identical to those of the PD group. Control subjects were excluded if they had been taking dopaminergic or central-acting anticholinergic agents. Control subjects were all on a general medical ward rather than a cardiology or peripheral vascular surgery service, and they were felt to be representative of the "usual" VA hospital patient. All patients in our institution have the same data base filed on admission and discharge by similarly trained staff, which adds to data uniformity.

All charts were inspected for the incidence of ischemic stroke, definite myocardial infarction, coronary arterial disease, arterial hypertension requiring antihypertensive medications, diabetes mellitus, tobacco use,
atrial fibrillation, congestive heart failure, malignant neoplasm, ethanolism, and dementia. Dementia was defined by a Folstein Mini-Mental State score of 25 or less or a chart documentation of progressive cognitive decline. The control population incidences were halved accordingly. The PD outpatient charts were also analyzed for the incidence of ischemic stroke and myocardial infarction until the day of data analysis to account for previous theories of PD providing neuroprotection from stroke. Specific criteria were required to establish the diagnosis of ischemic stroke and included documentation by the attending or consulting neurologist of prolonged or permanent neurological deficit, clinical history of ischemic stroke with computed tomography scan or magnetic resonance imaging confirmation, and no evidence of cerebral hemorrhage on neuroimages.

The cumulative incidence rates for ischemic stroke, myocardial infarction, coronary arterial disease, hypertension, diabetes, tobacco use, atrial fibrillation, heart failure, cancer, ethanolism, and dementia were determined in PD patients relative to control subjects. Z scores and probability values were determined by one-tailed Mantel-Haenszel tests.

**Results**

In addition to risk factor incidence in the PD patients, we also studied the severity of PD. Classified as having stage I in this study were 23.5% of the patients; stage II, 48.7%; stage III, 12.6%; stage IV, 12.6%; and stage V, 2.5%. Anti-PD agents being taken singularly or in combination were noted; 71% of the PD patients were taking carbidopa/levodopa, 11.8% bromocriptine, and 5.9% amantadine. In addition, 12.6% of the patients were taking anticholinergic agents and 1.7% selegiline.

The cumulative incidences of ischemic stroke, hypertension, and diabetes were not significantly different between groups (Figures 1 and 2). Myocardial infarction ($p=0.0516$), coronary arterial disease ($p=0.0008$), tobacco use ($p=0.0094$), atrial fibrillation ($p=0.0143$), cancer ($p=0.0001$), and ethanolism ($p=0.0001$) were all significantly more evident in control subjects. Congestive heart failure ($p=0.045$) and dementia ($p=0.0001$) were the only variables more evident in PD patients. The frequency of dementia in patients with PD was 31 of 119 (26%) versus nine of 119 (7.6%) in control subjects.

**Discussion**

The present study shows similar and disparate features from the work of Struck et al. In terms of demographics, the present study shows a group of PD patients of mean age 68.5 years (versus 66.9 years in the study of Struck et al) and a disease duration of 7.3 years (versus 7.7 years). Severity of PD is also comparable between studies: stage 1 patients in the present study represent 23.5% versus 20.5% in that of Struck et al; stage II, 48.7% versus 46.0%; stage III, 12.6% versus 23.5%; stage IV, 12.6% versus 8.5%; and stage V, 2.5% versus 1.5%. In addition, the specifics of anti-PD medications taken are similar between studies. This report is focused on male veterans with PD who were discharged from the Middleton VA Hospital, and the control subjects are non-PD patients discharged over the same period. This study also chose a 2-for-1 control population that is precisely, although randomly, matched for age and sex. Struck et al did not specifically control for age or sex, and they chose a dermatologic control population because of the anticipated similarity in age range relative to PD patients. Struck et al related that their control population's medical condition was not related to an increased incidence of atherosclerotic vascular disease. The present study's control population makes only the assumption that the controls were not hospitalized for ischemic stroke or myocardial infarction at the time of study entry but may well have had either during prior hospitalizations. Both the present study and that of Struck et al are retrospective in design and subject to the same methodological concerns. We believe, however, that our control group represents a logically chosen veteran population.

In this study, the cumulative incidence of ischemic stroke is not significantly different between PD patients and control subjects. Struck et al report a lower incidence of ischemic stroke in PD and believe it is related to less-severe generalized atherosclerosis. This lower stroke incidence in PD may, however, be related to the control group used. Our control group was more closely matched to our study group in that we accounted directly for age, male sex, and patient profile. Although Kessler reports that heart disease, stroke, and peptic ulcer were significantly less frequent in male PD cases, he also reports that hardening of the arteries is significantly elevated among those with PD. However, details of those conditions are not reported. Hoehn and Yahr, in their classic study, relate that although it is difficult to accurately evaluate the incidence of atherosclerosis in a population, the proportion of deaths due to vascular lesions of the brain is significantly higher in male PD patients 45–64 years of age compared with the general
population. The study of Hoehn and Yahr, while being one of the few studies that deal with causes of death in PD, is not designed for direct comparison with our study. Eadie and Sutherland\textsuperscript{3} fail to demonstrate a clinically estimated significant association between PD and atherosclerosis. Marttila and Rinne\textsuperscript{6} also find no significant differences between PD patients and control subjects concerning the occurrence of cardiac insufficiency, coronary arterial disease, or stroke. The mean patient age of 67.9 years, disease duration of 7.2 years, and severity of disease in their study are comparable with those in our present study. In addition, the cumulative incidence of ischemic stroke in their study is 1.16; this translates to a Z score of 0.71 and a probability value of 0.76 by the Mantel-Haenszel test. These values are remarkably similar to those reported in our present study. Thus, there is no overt protection from ischemic stroke in those with PD.

In the present study, the cumulative incidences of myocardial disease and diabetes are not significantly different between PD patients and control subjects, although in both our study and that of Struck et al\textsuperscript{2} the values for diabetes approach significance for a higher incidence in controls. No other studies report the incidence of diabetes. Struck et al report no significant difference in the incidence of hypertension between PD patients and control subjects. Marttila and Rinne\textsuperscript{6} report significantly less arterial hypertension in patients with PD, with a cumulative incidence that translates to a Z score of -3.2 and a probability value of 0.001. In a follow-up study, Marttila and Rinne\textsuperscript{11} report that PD patients had a lower systolic blood pressure and more rarely suffered from hypertension.\textsuperscript{11} However, no other study carefully relates specific blood pressure values.

In this study and that of Struck et al,\textsuperscript{2} the cumulative incidence of myocardial disease is significantly less in PD patients. Marttila and Rinne,\textsuperscript{6} however, report no difference in myocardial disease between PD patients and control subjects. The cumulative incidence of myocardial disease in their study translates to a Z score of 1.25 and a probability value of 0.11.

In our study and in that of Struck et al,\textsuperscript{2} the cumulative incidence of tobacco use is significantly less in PD patients. This particular relation is first alluded to by Kahn\textsuperscript{12} in 1966 and has held true in several other studies. Baron\textsuperscript{15} reports that smoking may actually be a protective exposure in relation to developing PD. Smoking facilitates dopamine release and dopaminergic neural transmission throughout the nervous system, which could delay or prevent the emergence of the clinical symptoms of PD in subjects whose dopaminergic functioning would otherwise drop below a symptom threshold.\textsuperscript{15}

In this study, the cumulative incidences of atrial fibrillation, cancer, and ethanolism are all significantly less in PD patients. No other study mentions atrial fibrillation. Hoehn and Yahr\textsuperscript{3} and Kessler\textsuperscript{4} report nonsignificant differences in cancer incidence between PD patients and control subjects. The Middleton VA Hospital, as part of a large regional cancer program of the University of Wisconsin, may have had a disproportionately high number of cancer patients discharged during the study period. Kessler\textsuperscript{4} and Baumann et al\textsuperscript{14} also both report nonsignificant differences in ethanolism between PD patients and control subjects.

In this study, the cumulative incidences of congestive heart failure and dementia are significantly higher in patients with PD. Whether the incidence of heart failure is related to anti-PD medications or to severity of disability is unclear and is in need of further study. It is not surprising to find that dementia is more evident in patients with PD. Concomitant cerebral atherosclerosis is reported to modify the natural course of PD, especially in the development of dementia.\textsuperscript{6,16,17} Our study finds a frequency of dementia in PD patients of 26%, which is quite similar to the 29% reported by Marttila and Rinne\textsuperscript{17} but somewhat lower than the 40% reported by Celesia and Wanamaker.\textsuperscript{16}
In conclusion, our study does not favor the concept that PD confers a specific protective benefit against ischemic stroke; neither do our data strongly favor an etiologic role for clinical atherosclerosis as a cause for PD. Prospective cohort, and possibly multicenter, studies will further clarify these issues.

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References

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