Previous studies have not agreed on the incidence of ischemic stroke in persons with Parkinson’s disease. There are epidemiologic and neurochemical facets of Parkinson’s disease that might confer some benefit or protection against ischemic stroke. We used a case-control method to determine the lifetime history of ischemic stroke in 200 patients with Parkinson’s disease and 200 controls of a similar age range. Analysis was also carried out for myocardial infarction as a marker of generalized atherosclerotic disease and for stroke risk factors. The cumulative incidence of ischemic stroke was significantly less in the patients with Parkinson’s disease than in the controls, as was the cumulative incidence of myocardial infarction. Among risk factors, significantly fewer patients with Parkinson’s disease used tobacco than controls. The decreased incidence of ischemic stroke in the patients with Parkinson’s disease appears to be related to their less severe generalized atherosclerosis, possibly due to their lower incidence of tobacco use. In view of the known potential for dopamine to exacerbate experimental ischemic tissue damage, the possibility that the dopamine deficiency in the central nervous system of persons with Parkinson’s disease confers an additional specific protective benefit against ischemic stroke cannot be excluded and requires further study. (Stroke 1990;21:1395–1399)
symptoms included carbidopa/levodopa in 154, bromocriptine in 24, and amantadine in 30 patients.

The control population consisted of persons >39 years of age undergoing a Mohs' procedure for removal of a skin carcinoma at the same institution. Information was again obtained by retrospective chart review of the last 200 patients. The mean age of the controls was 70.5 (range 42–95) years. There were 87 women and 113 men. This control population was chosen because of the anticipated similarity in age range relative to PD patients and because their medical condition is not related in any known way to an increased incidence of atherosclerotic vascular disease or ischemic stroke. Skin cancer patients on dopamine-blocking agents and those with a history of malignant melanoma or PD were excluded.

Data obtained by the physician caring for each subject included age at the time of the interview, sex, and history of ischemic stroke, myocardial infarction, hypertension, diabetes mellitus, and tobacco use (past or present). For PD patients, the duration and clinical stage of PD were recorded. If any information was incomplete, the subject was excluded. Approximately 10% of the total number of charts reviewed were excluded for this reason, leaving 200 valid charts for analysis.

Specific criteria were required to establish the diagnoses of ischemic stroke and myocardial infarction (Table 1). Subjects with infarct(s) noted on a cerebral computed tomographic (CT) scan that were clinically silent were considered not to have had an ischemic stroke because of the increased likelihood of PD patients having a clinically silent infarct noted on a CT scan performed during the course of the initial evaluation of their parkinsonian symptoms. For PD patients, lifetime stroke incidence was determined; that is, the charts were reviewed for the incidence of stroke both before and after the diagnosis of PD. Since considerable nigral degeneration antedates the clinical onset of PD,5 any protective benefit against stroke might be manifest both before and after the clinical diagnosis of PD. For consistency, the controls' lifetime stroke incidence was also determined by chart review. The occurrence of myocardial infarction as a marker of atherosclerotic vascular disease was determined in both patients and controls. The determination of hypertension was based on whether the subject's primary care physician felt antihypertensive medication(s) were necessary and had been initiated.

The cumulative incidences (life history rates) of ischemic stroke, myocardial infarction, hypertension, diabetes mellitus, and tobacco use were determined, as were the cumulative incidence ratio and odds ratio for each in PD patients relative to the controls. The Z scores associated with the cumulative incidence ratios were calculated according to Kleinbaum et al.6 For ischemic stroke, the probability values were calculated based on testing the null hypothesis against a single-tailed alternative hypothesis (that the incidence of ischemic stroke is reduced in PD patients relative to controls). To remain consistent, probability values for differences in the incidences of myocardial infarction, hypertension, diabetes mellitus, and tobacco use were also determined using a one-tailed test.

**Results**

The cumulative incidences of ischemic stroke, myocardial infarction, hypertension, diabetes mellitus, and tobacco use were greater in the controls than in the PD patients (Figure 1), but determination of the cumulative incidence ratios revealed significant differences only for ischemic stroke (p=0.029), myocardial infarction (p=0.0082), and tobacco use (p=0.0055) (Figure 2). Analyzed by calculating the odds ratios (data not shown), the occurrences of ischemic stroke, myocardial infarction, and tobacco use were again significantly increased in the controls.

**Discussion**

There are both epidemiologic factors and aspects of neurotransmitter function in PD that might affect the incidence or severity of ischemic stroke. Various neurotransmitters have been implicated in the etiopathogenesis of ischemic stroke,7,8 and several recent studies have concentrated on the role of dopamine.9-13 The neurotransmitter known to be deficient in PD. If there are inherent mechanisms protective against ischemic stroke in the CNS in PD, they may be related to altered dopamine function. Experimental catecholamine depletion protects the brain from ischemic damage.9-12,14-15 It is not yet known, however, whether the dopamine deficiency occurring in idiopathic PD similarly ameliorates the effects of cerebral ischemia. Increased extracellular catecholamine concentration during and after cerebral ischemia has been clearly established. During cerebral ischemia there is a massive release of dopamine.16-18 With reperfusion after ischemia, dopamine excess may persist for as long as 12 hours.19 This leads one to speculate whether this dopamine excess during recovery contributes to posts ischemic neuronal damage. While the exact mechanisms of dopamine release under these circumstances are unknown, cell membrane dysfunction due to ischemia-induced energy failure has been proposed as one possible cause.16
A number of mechanisms have been proposed to explain how catecholamines may exacerbate the cell damage produced by cerebral ischemia. One theory centers around the role of catecholamines in the production of free radicals, which can potentially damage cell membranes, proteins, essential sulfhydryl groups, and other tissue constituents. Oxidative free radical reactions probably occur during cerebral ischemia and subsequent reperfusion. Products of catecholamine oxidation can covalently bind to glutathione or sulfhydryl groups on proteins, inactivating cellular enzymes or damaging structural neuronal components. During catecholamine oxidation by molecular oxygen, two superoxide anions are formed that are potentially dangerous free radicals. Metabolism of catecholamine by the enzyme monoamine oxidase produces hydrogen peroxide, a free radical precursor, and catecholamines can reduce transition metals to oxidation states that can catalyze free radical production from hydrogen peroxide. This occurs upon reperfusion, when oxygen is available as a cofactor for monamine oxidase. Finally, dopamine can react with hydroxyl radicals and form 6-hydroxydopamine, a neurotoxin.

In the striatum, following transient ischemia, there is a relative glucose hypermetabolism combined with hypoperfusion. This uncoupling of metabolism and blood flow causes striatal injury. Prior striatal dopamine depletion diminishes the extent of striatal metabolism/blood flow uncoupling and decreases the amount of ischemic neuronal damage. Thus, postischemic dopaminergic hyperactivity may induce or permit early resumption of striatal glucose metabolism in the face of insufficient cerebral blood flow, thereby contributing to ischemic injury. Furthermore, dopamine release may further reduce blood flow or induce vasospasm.

A corollary of the putative protective benefit of dopamine deficiency is that any circumstance that enhances dopamine release or function might increase the incidence of ischemic stroke. In this case, dopamine release could further reduce blood flow or induce vasospasm.
regard, it has been postulated that the increased incidence of ischemic stroke during the morning hours may be related to the normal circadian cycle of CNS dopamine function, which may peak early in the day. While the dopamine deficiency of PD might limit the severity of ischemic tissue damage, it is not as clear why the deficiency would result in a lowered incidence of ischemic stroke such as we found. One possible explanation is that, in the face of dopamine deficiency, the extent of neuronal damage or dysfunction is sufficiently reduced that the resultant syndrome is below the threshold for clinical detection. Evaluation of the clinical severity, in addition to threshold detection of clinical occurrence, of ischemic stroke in PD patients may further elucidate the relation between these two conditions. Because of the very low incidence of ischemic stroke in PD patients, however, more subjects than we included will be needed to carry out this analysis.

Although these are valid hypothetical reasons to attribute the decreased incidence of ischemic stroke in PD patients to dopamine deficiency, our finding that the cumulative incidence of myocardial infarction is also reduced suggests that the lower incidence of ischemic stroke may be due to less severe generalized atherosclerosis rather than to specific CNS-protective mechanisms. In our PD patients, the reduced incidence of tobacco use, a known risk factor for atherosclerotic vascular disease, supports this notion.

The negative association between PD and tobacco use has been noted in previous studies. It remains unexplained, but several hypotheses have been suggested, including smoking-facilitated dopamine release. In view of the experimental evidence linking dopamine release to ischemic cerebral damage, it is interesting to speculate whether this enhanced release is still one more way in which tobacco use predisposes to the development of clinically apparent stroke.

The lower incidence of ischemic stroke in PD patients demonstrated in this study appears to be related to less severe generalized atherosclerosis. The lower incidence of tobacco use among PD patients may explain the difference in severity of atherosclerotic vascular disease (as measured by the incidence of myocardial infarction) between the two groups. Additionally, while not manifest as a difference in the incidence of hypertension at the time of ascertainment, there could have been a tendency for lower blood pressure among the patients since disease onset or treatment initiation secondary to the autonomic dysfunction inherent to PD or due to the hypertensive effect of anti-PD drugs. These findings do not preclude the possibility that specific protective mechanisms in the brains of persons with PD, particularly those mechanisms related to dopamine deficiency, also play a role in the ischemic stroke modification associated with this condition. Further study, especially of the severity of ischemic stroke in PD patients, may help determine the relative contribution of dopamine deficiency to this phenomenon. This contribution, if confirmed, could provide a rationale for pharmacologic intervention in ischemic stroke with dopamine-depleting or -blocking agents.

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References


**KEY WORDS** • Parkinson's disease • cerebral ischemia • dopamine
Stroke and its modification in Parkinson's disease.
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http://stroke.ahajournals.org/content/21/10/1395