Reduced Risk Factors for Vascular Disorders in Parkinson Disease Patients
A Case-Control Study

Giulio Scigliano, MD; Massimo Musicco, MD, PhD; Paola Soliveri, MD, PhD; Immacolata Piccolo, MD; Gabriele Ronchetti; Floriano Girotti, MD

Background and Purpose—Sympathetic hyperactivity is a contributing cause of vascular disorders because it increases blood pressure, blood sugar, and blood lipids. Pervasive compromise of the central and peripheral autonomic nervous systems is common in idiopathic Parkinson disease (IPD) resulting in reduced sympathetic and parasympathetic function. We hypothesized that IPD was associated with reduced prevalence of cardiovascular disease risk factors as a result of reduced sympathetic activity.

Methods—We performed a retrospective case-control study on 178 newly diagnosed consecutive IPD patients, and 533 age- and sex-matched controls with other neurological diseases seen over the same period at the same hospital. For each case and control the following were noted on admission: smoking, diabetes, hypertension, body mass index, serum glucose, plasma cholesterol, triglycerides and total lipid levels, and blood pressure.

Results—Diabetes, history of smoking, high blood pressure, high blood glucose, high blood cholesterol, and triglycerides were significantly less frequent in IPD than controls.

Conclusions—IPD is a natural model of impaired hypothalamic-pituitary-adrenal axis activity and generalized sympathetic denervation. We interpret the association of untreated IPD with reduced vascular diseases risk factors as attributable to reduced autonomic activity, suggesting that autonomic hyperactivity may be involved in the pathogenesis of vascular disorders. (Stroke. 2006;37:1184-1188.)

Key Words: cardiovascular disease ■ cerebrovascular disease ■ Parkinson disease ■ risk factors

Idiopathic Parkinson disease (IPD) is a multifaceted syndrome that may include behavioral, psychiatric, and autonomic disturbances, in addition to the classic extrapyramidal manifestations of tremor, rigidity and bradykinesia. Neuropathologically, IPD is characterized by neuronal depletion in the substantia nigra pars compacta and widespread occurrence of intraneuronal inclusions, the Lewy bodies. Since the first clinical description of IPD by James Parkinson, autonomic dysfunction has been recognized as a hallmark of the disease. Lewy bodies are found in most autonomic centers including the hypothalamus, the dorsal motor nucleus of the vagus, and the intermediolateral column, and also in structures outside the central nervous system, particularly the sympathetic and enteric ganglia, and adrenal medulla, indicating that both central and peripheral autonomic nervous systems are involved by the disease process.

Low basal autonomic activity and reactivity to stimuli are well-known clinical features of IPD. Constipation, reduced bowel movements, and sexual dysfunction are linked to parasympathetic cholinergic failure, whereas sympathetic noradrenergic failure is responsible for orthostatic hypotension. These manifestations may occur early in the disease course. The adrenal medulla is a major component of the autonomic nervous system, and its catecholamine content is severely depleted in IPD; low aldosterone secretion and renin activity in plasma are also observed. Furthermore, the circadian variations in plasma corticotropin (ACTH), cortisol, and catecholamines are less marked in IPD patients than in healthy subjects. In IPD patients basal plasma levels of ACTH and cortisol are normal, but the increase in the plasma levels of these substances is blunted after pituitary-adrenal axis stimulation. Autonomic nervous system activity underlies all human voluntary and involuntary actions. The parasympathetic has a calming effect on various aspects of heart activity but stimulates visceral function. Adreno-sympathetic activity increases heart rate, vasomotor tone, and blood pressure, and exerts a major stimulatory influence on carbohydrate and
fatty acid metabolism. High blood pressure, diabetes and dyslipidemia, well known risk factors for vascular diseases, may all be exacerbated by sympathetic over-activity.

In view of the potential role of sympathetic activity in exacerbating vascular disease risk factors and the sympathetic nervous system damage in IPD, we carried out a retrospective study to compare the prevalence of vascular risk factors in a group of patients without IPD.

Subjects and Methods

IPD Patients

Candidates were 201 consecutive IPD patients, identified retrospectively from clinical records as hospitalized for the first time from January 1970 to December 1987 at the C. Besta Neurological Institute, Milan, and followed as part of an ongoing mortality study. It is usual to admit patients with suspected PD for assessment and research purposes. IPD had been diagnosed not > 6 months before admission, before which none had received levodopa. IPD was diagnosed when bradykinesia was present with at least 2 of the following: tremor, rigidity and postural instability. An additional criterion was good response to L-3,4-dihydroxyphenylalanine (L-DOPA). We excluded atypical degenerative parkinsonisms (Parkinson-type multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration), and secondary parkinsonisms caused by medication side effects structural cerebral damage or known metabolic causes. The initial diagnosis was changed during follow-up in 23 patients (11.4%) who were excluded from the present study. Of the 178 IPD patients included in the study, 143 (80.3%) received cerebral neuroimaging examinations on first admission or during follow-up. The characteristics of these patients are summarized in Table 1. L-DOPA was initiated in almost all cases during hospitalization. Mean duration of disease from symptoms onset to diagnosis was about 16 months. Nearly 70% of the patients had akinesia as predominant symptom; the remaining 30% had the tremor predominant form of IPD. Disease severity was mild (Hoehn and Yahr stage I–II) in over 78% of patients.

Statistical Methods

We investigated the following variables in cases and controls: smoking, diabetes, hypertension, cerebrovascular disease, cardiovascular disease, and blood pressure, sugar, cholesterol, triglycerides and total lipids. Smoking, diabetes, hypertension, cerebrovascular and cardiovascular diseases were analyzed as dichotomous variables with no history or not present as reference categories. Blood pressure, blood sugar, cholesterol, triglycerides and total lipids were categorized into tertiles based on their distribution in controls, with lowest tertile as reference. Patients with diabetes or hypertension were assigned to the third tertile of blood sugar or blood pressure (systolic and diastolic), respectively. The strength of association between IPD and these variables was assessed by unconditional logistic regression analysis, in which age (categorized as <55, 55 to 64 and >64 years) and sex were covariates. Odds ratios (OR) were calculated from the regression coefficients; 95% CIs were obtained from the standard errors of the regression coefficients. Initially crude ORs were calculated separately for each variable. Subsequently, we performed forward stepwise multivariable analysis to evaluate the independent contribution of each variable to the risk of having IPD. We also analyzed linear trends of the risk of developing IPD in relation to sugar, triglycerides, total lipids, and cholesterol (in blood) and diastolic and systolic blood pressure, both in the crude and multivariable (where appropriate) analyses.

Results

The percentages of IPD patients and controls whose parents were reported as dying of cerebrovascular disease (21% versus 21.9%) and coronary heart disease (21.9% versus 23%) were closely similar, as were the proportions whose
parents had diabetes (15.9% versus 14.9%) and hypertension (28.3% versus 26.9%).

Mean age was 58.1 (SD 11.4) in IPD patients and 59.8 years (SD 10.2) in controls; 51.7% of cases and 48.3% of controls were males. Mean BMI was similar in cases (25.6) and controls (25.0). One IPD patient (0.5%) had transitory ischemic attack 5 years before; the corresponding figure for controls was males. Mean BMI was similar in cases (25.6) and controls (25.0). One IPD patient (0.5%) had transitory ischemic attack 5 years before; the corresponding figure for controls were 8 (1.5%) and 5 (0.9%), respectively. Four IPD patients (2.3%) and 11 controls (2.0%) had a history of coronary heart disease, 5 IPD patients (2.8%) and 15 controls (2.8%) had been hospitalized for previous myocardial infarction. Admission ECG showed signs of ischemic heart disease in 12 IPD patients (6.7%) and 40 controls (7.5%). Cerebral neuroimaging showed signs of vascular damage (lacunar infarcts, periventricular white matter changes) in 9/143 (6.3%) IPD and 14/165 (8.5%) controls.

Smoking, diabetes and hypertension were more frequent in control than IPD patients. Almost all (97%) diabetics (cases and controls) had type II diabetes. Mean blood levels of glucose, cholesterol, triglycerides and total lipids, and mean systolic and diastolic blood pressure, were all higher in controls than cases (Table 2). Univariate analysis showed that smoking, diabetes and hypertension were significantly asso-

### TABLE 2. Crude and Multivariable Risk Estimates (ORs) for IPD Patients Compared to non-IPD Controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>IPD</th>
<th>Crude OR** (95% CI)</th>
<th>Multivariable OR*** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of smoking</td>
<td>294 (55.2%)</td>
<td>74 (41.6%)</td>
<td>0.54 (0.37–0.78) P=0.001</td>
<td>*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>58 (10.9%)</td>
<td>6 (3.4%)</td>
<td>0.30 (0.13–0.72) P=0.007</td>
<td>*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>134 (25.1%)</td>
<td>28 (15.7%)</td>
<td>0.59 (0.37–0.92) P=0.022</td>
<td>*</td>
</tr>
<tr>
<td>Blood glucose, mg/dl</td>
<td>Mean (No. of cases)</td>
<td>91.5 (533)</td>
<td>85 (178)</td>
<td>0.71 (0.57–0.88) P=0.002$</td>
</tr>
<tr>
<td></td>
<td>1st tertile [52–82]</td>
<td>182 (34.1%)</td>
<td>78 (43.8%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2nd tertile [83–91]</td>
<td>173 (32.6%)</td>
<td>67 (37.6%)</td>
<td>0.89 (0.60–1.31)</td>
</tr>
<tr>
<td></td>
<td>3rd tertile [92–233]</td>
<td>172 (32.3%)</td>
<td>33 (18.5%)</td>
<td>0.47 (0.29–0.75) P=0.001</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>Mean (No. of cases)</td>
<td>230.6 (345)</td>
<td>220 (111)</td>
<td>0.89 (0.68–1.15) P&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>1st tertile [93–208]</td>
<td>119 (34.5%)</td>
<td>46 (41.4%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2nd tertile [209–251]</td>
<td>112 (32.5%)</td>
<td>30 (27.0%)</td>
<td>0.70 (0.41–1.18)</td>
</tr>
<tr>
<td></td>
<td>3rd tertile [252–464]</td>
<td>114 (33.0%)</td>
<td>35 (31.5%)</td>
<td>0.79 (0.48–1.33)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>Mean (No. of cases)</td>
<td>151.0 (322)</td>
<td>134 (100)</td>
<td>0.65 (0.49–0.87) P=0.004$</td>
</tr>
<tr>
<td></td>
<td>1st tertile [45–116]</td>
<td>111 (34.5%)</td>
<td>48 (48.0%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2nd tertile [117–160]</td>
<td>104 (32.3%)</td>
<td>31 (31.0%)</td>
<td>0.70 (0.41–1.19)</td>
</tr>
<tr>
<td></td>
<td>3rd tertile [161–535]</td>
<td>107 (33.2%)</td>
<td>21 (21.0%)</td>
<td>0.42 (0.23–0.76) P=0.004</td>
</tr>
<tr>
<td>Total lipids, mg/dl</td>
<td>Mean (No. of cases)</td>
<td>828.2 (299)</td>
<td>761 (94)</td>
<td>0.71 (0.53–0.95) P=0.010$</td>
</tr>
<tr>
<td></td>
<td>1st tertile [433–717]</td>
<td>99 (33.1%)</td>
<td>42 (44.7%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2nd tertile [718–867]</td>
<td>101 (33.8%)</td>
<td>32 (34.0%)</td>
<td>0.79 (0.46–1.37)</td>
</tr>
<tr>
<td></td>
<td>3rd tertile [868–1700]</td>
<td>99 (33.1%)</td>
<td>20 (21.3%)</td>
<td>0.49 (0.27–0.90) P=0.021</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>Mean (No. of cases)</td>
<td>145.9 (530)</td>
<td>142 (177)</td>
<td>0.80 (0.64–0.99) P=0.041$</td>
</tr>
<tr>
<td></td>
<td>1st tertile [95–130]</td>
<td>173 (32.6%)</td>
<td>74 (41.8%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2nd tertile [131–150]</td>
<td>151 (28.5%)</td>
<td>51 (28.81%)</td>
<td>0.84 (0.54–1.29)</td>
</tr>
<tr>
<td></td>
<td>3rd tertile [151–240]</td>
<td>206 (38.9%)</td>
<td>52 (29.4%)</td>
<td>0.63 (0.41–0.98) P=0.041</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>Mean (No. of cases)</td>
<td>89.0 (530)</td>
<td>87 (177)</td>
<td>0.84 (0.69–1.03) P&gt;0.05§</td>
</tr>
<tr>
<td></td>
<td>1st tertile [50–80]</td>
<td>206 (38.9%)</td>
<td>76 (42.9%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2nd tertile [81–90]</td>
<td>118 (22.3%)</td>
<td>53 (29.9%)</td>
<td>1.28 (0.84–1.96)</td>
</tr>
<tr>
<td></td>
<td>3rd tertile [91–140]</td>
<td>206 (38.9%)</td>
<td>48 (27.1%)</td>
<td>0.68 (0.44–1.04)</td>
</tr>
</tbody>
</table>

*ORs absent for variables not included in multivariable regression analysis; §Numbers in square brackets are tertile ranges; **Crude ORs are adjusted for age and sex; ***Multivariable ORs are derived from a stepwise procedure that considered age, sex, smoking, diabetes, hypertension, blood sugar, cholesterol, triglycerides, total lipids, systolic and diastolic blood pressure; §ORs and P values for linear trend of association between the variable and the risk of having IPD.
ciated with reduced risk of having IPD. Furthermore, the risk of IPD was significantly lower in the third tertile of cholesterol, triglyceride and total lipid levels than the first tertile. The risk of having IPD was also significantly lower in the third tertile of systolic blood pressure compared with the lowest tertile, whereas diastolic blood pressure did not differ significantly between IPD cases and controls. Analysis of linear trends supported the analysis by categories, showing that ORs for having IPD significantly reduced with increasing blood sugar, triglycerides, total lipids and systolic blood pressure (Table 2). By contrast, $P$ values for trend of diastolic pressure and cholesterol were not significant.

When we carried out the stepwise multivariable analysis, smoking, diabetes, hypertension, cholesterol, total lipids and diastolic blood pressure were no longer significantly associated with reduced risk of having IPD. By contrast, blood glucose in the highest tertile (OR 0.49; 95% CI, 0.27 to 0.89), triglycerides in the highest tertile (OR 0.48; 95% CI, 0.27 to 0.88), and systolic blood pressure in the highest tertile (OR 0.52; 95% CI, 0.29 to 0.95) were significantly associated with reduced risk of IPD compared with the lowest tertile.

**Discussion**

This case-control study shows that untreated IPD patients at early disease stage were characterized by a lower prevalence of vascular risk factors than matched non-IPD controls. By univariable analysis we found that diabetes and hypertension, as well as high values of blood pressure, serum glucose, cholesterol, triglycerides and total lipids, were significantly less frequent in IPD patients than controls. The multivariable findings indicated that high systolic blood pressure, high blood glucose and high blood triglycerides were each associated with reduced risk of having IPD, independently of each other and independently of other laboratory variables measured at admission. Probability values for linear trends also indicated that ORs for developing IPD significantly reduced with increasing blood sugar, triglycerides, total lipids and systolic blood pressure.

This observational study is susceptible to bias arising from the fact that the hospital controls were unwell and might have an abnormally high prevalence of vascular risk factors than matched non-IPD controls. We therefore examined the tertile distribution of the variables inversely associated with IPD in the 3 control subgroups ("spinal," anxiety and depression, and other neurological diseases). The variables were evenly distributed across tertiles in each of the control groups. The least even distribution was that of systolic blood pressure, where the third tertile contained 28% of depression and anxiety patients, 33% of "spinal" patients and 34% of patients with other neurological disorders.

Another possible confounding effect could arise from different illness duration in cases and controls. We included newly diagnosed cases, whereas controls were recruited from those at first admission to our Institute. For this reason most (92.3%) controls were newly diagnosed and all had disease durations of <2 years. We therefore exclude that disease duration could have influenced the distribution of vascular risk factors between cases and controls.

We used age-adjusted ANOVA in cases to investigate whether disease duration was associated with blood pressure, glucose and triglycerides. We found that mean disease duration did not differ across tertiles of blood glucose and triglycerides but that mean disease duration differed significantly across blood pressure tertiles (1.17 months in lowest, 2.9 months in middle and 2.3 months in upper tertile). We cannot exclude that the negative association of IPD with vascular risk factors found in our study might become more pronounced with disease progression; however, our data pertain to patients with very short disease duration.

The reduced prevalence of vascular risk factors in IPD patients might be attributable to different diet compared with controls. However, BMI was closely similar in the 2 groups, so presumably energy intake was similar also. Furthermore a study on IPD patients in our catchment area (Region of Lombardy) found no evidence of BMI differences between Parkinsonians and the normal population.

The main findings of our study are plausibly explained by the reduced sympathetic activity amply documented in IPD. The sympathetic nervous system is permanently active in maintaining homeostasis, and is further activated during stress, physical activity, and whenever the body is stimulated. In response to such stimulations, the hypothalamic-pituitary-adrenal axis secretes ACTH, cortisol and catecholamines. Cortisol and catecholamines have multifarious effects on carbohydrate and lipid metabolism. Cortisol mobilizes fatty acids from adipose tissue, antagonizes insulin-mediated inhibition of liver glucose release, decreases glucose use in muscle and reduces the affinity of insulin receptors for insulin. Catecholamines, leaked from the brain and released by peripheral sympathetic neurons and the adrenal medulla, activate $c$AMP in liver, muscles and adipose tissue, stimulating glycogenolysis and resulting in increased plasma glucose and lipids. The sympathetic nervous system also plays a pivotal role in the genesis of hypertension, and many patients with hypertension have increased sympathetic tone, with increased plasma and cerebrospinal fluid norepinephrine. Norepinephrine is released from adrenergic autonomic fibers and the adrenal medulla, and acts on $\alpha$-receptors stimulating the heart, increasing basal tone and increasing renal vascular resistance, renin release and sodium retention.

In IPD, the hypothalamic-pituitary-adrenal axis is compromised, even in patients without clinically evident autonomic failure. Generalized sympathetic denervation is common, with decreased catecholamine content of the adrenal medulla, blunted circadian rhythms of circulating cortisol, and reduced levels of renin and aldosterone, while cardiac and blood vessel sympathetic innervation is also damaged.

The lower blood pressure in our IPD patients than controls likely results from sympathetic denervation of the heart, blood vessels and kidneys, and from involvement of adrenal medulla in the disease process. The lower blood glucose and triglyceride levels in our IPD patients compared with controls are also consistent with reduced catecholamine and cortisol production, and the reduced responses to stress stimuli observed in IPD.

In agreement with many other reports, smoking was less prevalent in the IPD patients than controls. Reduced smoking in IPD patients is usually interpreted as a consequence of...
premorbid personality and may also contribute to the lower lipid levels found in our IPD patients.24

Previous studies on vascular disorders in IPD have produced contrasting results: some found reduced cumulative incidence of ischemic stroke and myocardial infarction;25 others reported reduced incidence of infarction but not of ischemic stroke.26 The situation is complicated by the fact that most IPD patients are treated with levodopa, which increases blood homocysteine, and high levels of homocysteine are associated with increased incidence of cerebrovascular and cardiovascular disorders.27 The present study, carried-out on newly diagnosed and untreated patients with IPD, provides support for the hypothesis that the autonomic nervous system plays a role in the genesis of vascular disorders, as decreased sympathetic activity reduces important cardiovascular disease risk factors, such as hypertension, diabetes and dyslipidemia. From the clinical point of view this will probably not translate into a major decrease in cerebrovascular and cardiovascular disorders in view of the dopaminergic treatment that Parkinsonians receive for their disease.

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References
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