Background: It is accepted that orthostatic hypotension is a clinical marker for the diagnosis of multiple system atrophy, but conflicting data indicate that it may also be present in Parkinson disease (PD).

Objectives: To evaluate the prevalence of autonomic cardiovascular impairment and orthostatic hypotension in a large group of patients with de novo PD, followed up for at least 7 years, to clinically confirm the diagnosis of the disease.

Methods: During a 2-year recruiting period, 60 untreated patients diagnosed as having idiopathic PD underwent autonomic cardiovascular function evaluation using the Ewing test. Patients subsequently received dopaminergic therapy and their condition was followed up for at least 7 years.

Results: Nine (15%) of 60 patients were excluded from the study because during the follow-up period a parkinsonian syndrome was diagnosed (5 had multiple system atrophy and 4 had progressive supranuclear palsy). Data from 51 patients with PD underwent final statistical analysis and the results were compared with those of 51 age-matched healthy control subjects who had taken the same battery of autonomic tests. A statistically significant difference was found in postural hypotension ($P\text{ = .02}$) and deep breathing test results ($P\text{ = .03}$) between patients and controls. Seven (14%) of 51 patients with PD and 3 (60%) of 5 patients with multiple system atrophy had a decrease of more than 20 mm Hg in systolic blood pressure on standing.

Conclusions: Data from this study indicate a high prevalence of sympathetic and parasympathetic failure in patients with de novo PD, and when using a decrease of at least 20 mm Hg in systolic blood pressure, manometric orthostatic hypotension was found in 7 (14%) of the 51 patients with de novo PD.

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Autonomic dysfunction and impaired cardiovascular response to postural changes, particularly orthostatic hypotension (OH), are considered important clinical markers for the diagnosis of multiple system atrophy (MSA) and are incorporated in the main clinical criteria for the diagnosis of this disease.$^{1,4}$ It is accepted that OH is also a common finding of idiopathic Parkinson disease (PD), which is the more frequent alternative diagnostic hypothesis to MSA.$^{5,8}$ Results of neuropathological studies indicate that the autonomic nervous system is involved in PD. In fact, Lewy bodies sometimes associated with neuronal loss can be found in central and peripheral structures involved in autonomic regulation.$^{9,12}$ However, the appearance and severity of autonomic symptoms could be clinically relevant with respect to the disease onset. In clinical-pathological retrospective studies, earlier and more severe OH has been reported in patients who have confirmed MSA compared with patients who have PD.$^{13,14}$

Clinical studies on autonomic dysfunction in PD have produced conflicting results. In most studies cardiovascular autonomic failure occurs only several years after the onset of disease, often in elderly patients.$^{15,16}$ While in a few studies conducted in small groups of treated or untreated patients with PD, cardiovascular autonomic impairment and OH have been reported in the early stage of the disease.$^{17,18}$ The inclusion of patients treated with dopaminergic agents,$^{16,19,20}$ anticholinergics,$^{16,19,20}$ and amantadine hydrochloride$^{20,22}$ may have determined these discrepancies. Furthermore, none of the aforementioned studies included a follow-up period sufficiently long enough to clinically confirm the diagnosis of PD and the exclusion of other primary parkinsonian syndromes.
isms, mainly MSA. The aim of this study was to evaluate the presence of OH and cardiovascular autonomic dysfunction in patients with de novo PD whose diagnosis was clinically confirmed after a follow-up period of at least 7 years.

METHODS

During a 2-year period (January 1, 1993, through December 31, 1994), 60 (29 men and 31 women) consecutive untreated patients (mean age [SD], 53.2 [9.4] years) diagnosed as having idiopathic PD in accord with the arbitrarily amended criteria of the United Kingdom Brain Bank were studied. Early autonomic involvement including the occurrence of nonsympathetic OH—defined as a minimum decrease in systolic and/or diastolic blood pressure of 20 mm Hg or 10 mm Hg, respectively, on standing at the third minute—was not considered an exclusionary criterion for the diagnosis of idiopathic PD unless it was associated with atypical signs and symptoms suggestive of other parkinsonian syndromes. As supporting criteria, a magnetic resonance imaging scan and the acute challenge test using levodopa were performed in each patient at the first evaluation.

All subjects underwent autonomic function evaluation using the classic Ewing cardiovascular tests.24 Patients with diseases causing secondary dysautonomia, such as hypertension, diabetes mellitus, gastrointestinal tract diseases, and other cardiovascular diseases or impaired hepatic or renal function, or those taking medication known to affect the autonomic nervous system had been previously excluded, as well as patients with a history of psychiatric disorders, cognitive impairment, or other neurological diseases. Disease severity was scored at baseline according to the Unified Parkinson’s Disease Rating Scale (UPDRS)25 and the Hoehn and Yahr scale.26 Fifty-one sex- and age-matched healthy controls who underwent autonomic cardiovascular tests. None of the population studied are listed in Table 2.

A follow-up period of at least 7 years (December 31, 2001 was considered the end of this period) took place during which dopamine agonists and, when necessary, levodopa therapy were given. This long follow-up period was chosen to exclude those patients developing atypical signs of disease and those without a dopaminergic response, suggesting a parkinsonian syndrome other than PD.

During this follow-up period, patients were evaluated every 4 months; at each visit a standardized neurological examination was performed and the UPDRS and Hoehn and Yahr scales were completed to assess the patient’s clinical disability. A second magnetic resonance imaging scan and/or a re-evaluation of autonomic test results, sphincteric electromyography, and neuropsychological testing were performed when a diagnosis other than PD was suggested during the follow-up period.

AUTONOMIC TESTS

Cardiovascular autonomic nervous function was investigated under standardized conditions using cardiovascular reflexes. Three of 5 tests (responses to the Valsalva maneuver, deep breathing, and standing up) were based on the measurement of heart rate (HR) changes while the other 2 tests (responses to standing up and sustained handgrip) depended on arterial blood pressure (BP) measurements.

Heart rate response to the Valsalva maneuver was expressed as the Valsalva ratio (ie, the longest R-R interval after the Valsalva maneuver divided by the shortest R-R interval during the Valsalva maneuver) that is taken as the mean ratio from 3 successive Valsalva maneuvers. Heart rate response to standing up or “lying to standing” was expressed by the 30:15 ratio (longest R-R interval around the 30th heart beat after standing up divided by the shortest R-R interval around the 15th heart beat). Heart rate response to deep breathing was measured as the maximum HR minus the minimum HR during 10-second breathing cycles. After 3 successive breathing cycles, a mean of the differences between the maximum HR and minimum HR was calculated.

Arterial BP response to standing up or the OH test was performed by measuring the arterial BP after the patient had been at rest in the supine position for 10 minutes, and again after 3 minutes of standing up. The difference between systolic and diastolic BP was taken as the measurement of postural BP change. Arterial BP response to sustained handgrip was measured as the difference between the diastolic BP just before releasing and before starting the handgrip.

STATISTICAL ANALYSIS

Comparisons were performed by 1-way analysis of variance and the Welch analysis of variance for quantitative variables; the $\chi^2$ test was used for qualitative variables. $P<.05$ was considered statistically significant.

Nine (15%) of 60 enrolled patients diagnosed as having idiopathic PD in accord with the arbitrarily amended criteria of the United Kingdom Brain Bank (see “Methods” section) were excluded from the final analysis because atypical signs appeared and a lack of response to dopaminergic therapy occurred during the follow-up period, allowing for the diagnosis of MSA in 5 patients and progressive supranuclear palsy (PSP) in 4 patients. During the follow-up period, the 5 patients whose final diagnosis was MSA developed a rapid progression of the disease with marked dysautonomia, corticospinal tract dysfunction in 2 patients, erectile dysfunction in 2 patients, urgency and urinary incontinence in 2 patients, and a slitlike magnetic resonance imaging-signal change at the posterolateral putaminal margin in 3 patients. Abnormal sphincteric electromyographic patterns were found in all 5 patients. During the follow-up period, the 4 patients whose final diagnosis was PSP had supranuclear vertical down-gaze palsy, 3 patients had axial dystonia, and 2 patients had frontolimbic dementia.

Fifty-one patients entered the final statistical analysis and were compared with 51 sex- and age-matched healthy controls who underwent assessment using the same battery of autonomic cardiovascular tests. None of the controls had any disease or took medication known to affect the autonomic nervous system. Characteristics of the population studied are listed in Table 1.

Patients with PD showed a significant impairment of HR response to the deep breathing test compared with the controls ($P=.03$) (Table 2); furthermore, the results of the OH test revealed a significant decrease in orthostatic BP in patients with PD ($P=.02$) (Table 2). Results of the remaining tests disclosed no cardiovascular autonomic abnormalities (Table 2). A comparison of the supine systolic and diastolic BP revealed significant differences between patients with PD and controls ($P<.01$) while no differences were observed in the HR when the subjects were in the supine position.

Seven (14%) of 51 patients with PD and 3 (60%) of 5 patients with MSA had a decrease of more than
The presence of early cardiovascular autonomic impairment and OH in PD could make the diagnosis of idiopathic PD uncertain, evoking in particular MSA. There are no clear-cut clinical criteria allowing physicians to discard MSA from idiopathic PD, especially in the early stages of the diseases, as repeatedly shown by clinicopathological study findings. A good, sustained response to dopaminergic treatment and lack of additional neurological features during the 7-year follow-up allowed us to confirm the diagnosis of idiopathic PD. A 7-year follow-up would be sufficient to exclude disorders such as MSA or PSP that usually progress more rapidly than typical cases of PD. We found that 9 (15%) of 60 patients initially diagnosed as having PD had an alternative diagnosis at the end of the follow-up of at least 7 years (mean, 7.9 years). This figure is close to that of Jankovic et al. who reported that after a mean 6-year follow-up period, the initial clinical diagnosis based on the criteria of the DATATOP study was incorrect in 8.1% of patients.

Although OH is considered one of the hallmarks of MSA, it may be present in patients with PD. Data from retrospective studies show differences in the frequency and severity of autonomic dysfunction between MSA and PD; symptomatic OH occurring within 1 year of disease onset predicted the diagnosis of MSA in 75% of patients. In a more recent study evaluating cardiovascular reflexes in patients with MSA and PD, impairment of cardiovascular reflexes was found at all ages and within a short disease duration in the MSA group, whereas pathological autonomic reactions were found at an older age and after a long disease duration in patients with PD.

Several limitations of this clinical study should be stressed,

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**Table 1. Characteristics of the Populations Studied**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With PD (n = 51)</th>
<th>Control Subjects (n = 51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.2 (8.9)</td>
<td>54.6 (8.9)</td>
<td>.56</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>29/22</td>
<td>31/20</td>
<td>.51</td>
</tr>
<tr>
<td>Duration of disease, mo</td>
<td>22.2 (14.4)</td>
<td>NA</td>
<td>.45</td>
</tr>
<tr>
<td>Hoehn and Yahr score</td>
<td>1.2 (0.3)</td>
<td>NA</td>
<td>.68</td>
</tr>
<tr>
<td>UPDRS parts II/III scores†</td>
<td>7.6/14.9</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PD, Parkinson disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

†The UPDRS parts II/III assesses activities of daily living and motor function, respectively.

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**Table 2. Cardiovascular Autonomic Tests in Patients With De Novo PD Whose Diagnosis Was Clinically Confirmed After a Follow-up of at Least 7 Years**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Patients With PD (n = 51)</th>
<th>Control Subjects (n = 51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH, Δ mm Hg</td>
<td>-9.4 (9.5)</td>
<td>-1.0 (5.4)</td>
<td>.02</td>
</tr>
<tr>
<td>SH, Δ mm Hg</td>
<td>24.0 (10.1)</td>
<td>25.4 (7.9)</td>
<td>NS</td>
</tr>
<tr>
<td>DB, Δ breaths/min</td>
<td>16.1 (8.0)</td>
<td>20.1 (7.9)</td>
<td>.03</td>
</tr>
<tr>
<td>VR ratio†</td>
<td>1.6 (0.3)</td>
<td>1.6 (0.3)</td>
<td>NS</td>
</tr>
<tr>
<td>LTS ratio</td>
<td>1.3 (0.1)</td>
<td>1.2 (0.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: DB, deep breathing; LTS, lying to standing; NS, not significant; OH, orthostatic hypotension; PD, Parkinson disease; SH, sustained handgrip; VR, Valsalva ratio; Δ, change.

†The VR ratio is calculated as follows: the longest R-R interval after the Valsalva maneuver is divided by the shortest R-R interval during the Valsalva maneuver, which is taken from the mean ratio of 3 successive Valsalva maneuvers.

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**Table 3. Baseline Cardiovascular Autonomic Test Results in Patients Reclassified to Have MSA or PSP**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Patients With MSA (n = 5)</th>
<th>Patients With PSP (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH, Δ mm Hg</td>
<td>-24.8 (11.0)</td>
<td>-7.0 (3.5)</td>
</tr>
<tr>
<td>SH, Δ mm Hg</td>
<td>24.0 (8.9)</td>
<td>25.0 (5.0)</td>
</tr>
<tr>
<td>DB, Δ breaths/min</td>
<td>16.0 (7.9)</td>
<td>20.9 (5.8)</td>
</tr>
<tr>
<td>VR ratio†</td>
<td>1.5 (0.2)</td>
<td>1.6 (0.2)</td>
</tr>
<tr>
<td>LTS ratio</td>
<td>1.3 (0.1)</td>
<td>1.2 (0.1)</td>
</tr>
</tbody>
</table>

Abbreviations: DB, deep breathing; LTS, lying to standing; MSA, multiple system atrophy; OH, orthostatic hypotension; PSP, progressive supranuclear palsy; SH, sustained handgrip; VR, Valsalva ratio; Δ, change.

†The VR ratio is calculated as follows: the longest R-R interval after the Valsalva maneuver is divided by the shortest R-R interval during the Valsalva maneuver, which is taken from the mean ratio of 3 successive Valsalva maneuvers.

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20 mm Hg in systolic BP on standing. Symptoms of hypotension occurred in only 1 patient with PD, while 3 of 5 patients with MSA experienced symptomatic hypotension. Findings from baseline cardiovascular autonomic tests that resulted in the reclassification of patients as having MSA or PSP are summarized in Table 3. No postural decrease in arterial BP was observed in patients with PSP (Figure). Systolic and diastolic BP of the subgroup of patients with PD and OH were statistically significantly higher compared with the remaining patients with PD who did not have OH (P = .03).
particularly the presence of concomitant antiparkinson treatments and the lack of follow-up to confirm the clinical diagnosis. Conversely, our data support the presence of OH values in a considerable proportion of patients with PD in the early stages of the disease. Recently, in a retrospective study of autonomic nervous system testing, no difference was found between PD and MSA in formal laboratory testing, including evaluation of the decrease in systolic BP that was present in most patients. 33 Although the study included patients with both early and advanced disease stages, Riley and Chelimsky 34 suggest that current clinical criteria for PD and MSA based on the presence of dysautonomia may be inappropriate.

Recent studies have agreed that patients with PD have a high prevalence of loss of sympathetic innervation of the heart. 34,35 It has been hypothesized that generalized sympathetic denervation would provide an explanation for OH. A recent positron emission tomographic study visualizing sympathetic innervation after injection of fludeoxyglucose F 18 has demonstrated that OH in PD reflects sympathetic neurocirculatory failure from generalized sympathetic denervation. 36

According to previous data, 37 patients with PD and OH showed high readings for supine systolic and diastolic BP. The high supine systolic and diastolic BP found in these patients have been attributed to a supersensitivity of vascular α-adrenergic receptors and may represent an attempt to palliate orthosympathetic failure in patients with PD and OH. 37

CONCLUSIONS

Data from this study indicate that (1) quite a high prevalence of sympathetic and parasympathetic failure occurs in patients with de novo PD and (2) when using a decrease of at least 20 mm Hg in systolic BP, 14% of the patients with de novo PD had manometric OH. These data induce us to comment on the importance of the criteria for defining OH and their use for the diagnosis of PD and MSA. Although manometric OH is more common in early MSA than in early PD, the presence of a decrease of more than 20 mm Hg in systolic BP on standing cannot exclude the diagnosis of idiopathic PD in the early stages of the disease.

Finally, the frequent presence of OH in patients with de novo PD that emerges from this and other studies 6,8 may be relevant to the therapeutic options in early PD. A recent report showed that acute OH occurs frequently when starting dopamine agonist therapy in patients with PD. 36 Since dopamine agonist monotherapy is highly recommended in patients with de novo PD to avoid or delay the appearance of levodopa-induced dyskinesias and motor fluctuations, 39,40 we suggest carefully monitoring the supine and orthostatic BP in such patients and, if appropriate, adding domperidone, or slowly titrating the dose of the drug.

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Author contributions: Study concept and design (Drs Bonuccelli and Lucetti); acquisition of data (Drs Gambaccini, Bernardini, and Piaggesi); analysis and interpretation of data (Drs Bonuccelli, Del Dotto, Ceravolo, Gambaccini, Rossi, and Piaggesi); drafting of the manuscript (Drs Bonuccelli, Lucetti, Gambaccini, and Bernardini); critical revision of the manuscript for important intellectual content (Drs Bonuccelli, Del Dotto, Ceravolo, Rossi, and Piaggesi); statistical expertise (Dr Rossi); administrative, technical, and material support (Drs Lucetti, Del Dotto, Gambaccini, Bernardini, and Piaggesi); study supervision (Drs Bonuccelli and Ceravolo).

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