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Combined Use of DAT-SPECT and Cardiac MIBG Scintigraphy in Mixed Tremors

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Abstract: The cooccurrence of rest and postural tremor (mixed tremor) as the predominant clinical manifestation in patients who do not fulfill diagnostic established criteria for essential tremor (ET) or Parkinson's disease (PD) poses a clinical diagnostic challenge. Twenty-two patients with mixed tremor and additional mild extrapyramidal features, such as bradykinesia and rigidity, 20 patients with probable PD, 10 patients with probable ET, and 18 controls were investigated through the combined use of dopamine transporter ^{123}I-FP-CIT-single-photon emission tomography (DAT-SPECT) and cardiac ^{123}metaiodobenzylguanidine (MIGB) scintigraphy. Six of the 22 mixed-tremor patients had normal DAT-SPECT, a condition usually found in patients with ET, whereas 16 patients showed damage to the nigrostriatal system. Cardiac MIBG allowed further differentiation between these 16 patients because eight of them had decreased tracer uptakes (heart/mediastinum [H/M] ratio in delayed image, H/M ratio delayed: 1.16 ± 0.11, $P < 0.001$ vs controls), indicating a PD, whereas the remaining eight had normal cardiac tracer uptakes, a finding suggestive of a parkinsonian syndrome (H/M ratio delayed: 1.90 ± 0.13). Both DAT-SPECT and cardiac MIBG scintigraphies were abnormal in the 20 patients with probable PD, whereas these were normal in both the patients with probable ET as well as in the controls. Our study suggests that the combined use of both DAT-SPECT and MIBG scintigraphy in mixed tremors with additional extrapyramidal features can help distinguish patients with ET from those with PD and parkinsonism. © 2009 Movement Disorder Society

Key words: MIBG scintigraphy; DAT-SPECT; mixed tremors

Rest tremor is one of the characteristic features of Parkinson's disease (PD), whereas essential tremor (ET) is characterized by postural and kinetic tremor. However, the overlap among tremor disorders is wide and complex because patients with ET may present resting tremor coexisting with postural tremor in about 18% of cases[1] and postural tremor may coexist with resting tremor in PD.[2] A combination of postural and rest (mixed) tremor is not uncommon, and when occurs as the sole (isolated mixed tremors) or predominant clinical manifestation, i.e., in addition to extrapyramidal features (mixed tremor plus), makes diagnosis uncertain.

Dopamine transporter ^{123}I-FP-CIT-single-photon emission tomography (DAT-SPECT) imaging can differentiate PD, where dopamine deficit is demonstrated, from ET where no dopamine deficit is usually found.[3,4] DAT-SPECT, however, is not able to distinguish between PD and atypical parkinsonian syndromes. Recently, several studies have emphasized the usefulness of myocardial scintigraphy with ^{123}metaiodobenzylguanidine (MIGB) in assessing the sympathetic

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nerve terminals in PD, demonstrating that cardiac MIGB uptake is strongly decreased in patients with this disease in comparison with patients with parkinsonism in which MIBG uptake is normal.[5,6]

The aim of this study was to evaluate whether the combined use of DAT-SPECT and cardiac MIBG scintigraphy in mixed tremors with mild extrapyramidal signs can help distinguish patients with ET from those with PD or parkinsonism.

PATIENTS AND METHODS

Patients

The study sample consisted of 22 consecutive patients with mixed tremor, 20 patients with a diagnosis of idiopathic probable PD (according to established clinical criteria[7]), 10 patients with probable ET (according to the Consensus criteria of the Movement Disorder Society on tremor[8]), and 18 control subjects. Patients with mixed tremor were enrolled whether they had postural and rest tremor as the prevalent feature with mild bradykinesia or rigidity (mixed tremor plus), and whether they showed poor levodopa response to an acute challenge. None of the mixed-tremor patient fulfilled diagnostic criteria for probable PD[7] or probable ET.[8] Every patient underwent an accurate clinical history and a videotaped neurological examination. A family history was considered positive when a first-degree relative was reported to be affected by postural or rest tremor. Clinical evaluation and tremor score were calculated according to the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS-ME). In all patients, global cognitive status was assessed through the Mini Mental State Examination (MMSE).[9] Every enrolled patient underwent an oral acute test with 250 mg of levodopa that was considered positive when the clinical improvement was 30% or greater of the baseline value on UPDRS-ME. The patients with damage to the dopaminergic pathway on DAT-SPECT were treated with levodopa and then followed-up clinically (UPDRS-ME) to evaluate chronic levodopa responsiveness. Imaging studies including brain magnetic resonance imaging (MRI), DAT-SPECT, and myocardial MIGB scintigraphy were assessed in all patients and in control subjects. Autonomic testing was performed in all patients.[10] No subject had any history of cerebrovascular diseases, other degenerative neurological diseases or intracranial lesions in brain MRI, thyroid diseases, diabetes mellitus, previous relevant cardiac disease, or any other medical condition that could affect the autonomic nervous system or the myocardial MIBG. No subject was taking drugs known to interfere with MIBG uptake in sympathetic nerve terminals.

The study was approved by the Institutional Ethics Committee, and all participants gave written informed consent.

^{123}I-FP-CIT Studies

All patients received perchlorate (1000 mg) 30 minutes before being scanned to block thyroid uptake free radioactive iodine. Brain imaging was performed 3 hours after the administration of 200 MBq of ^{123}I-FP-CIT (GE-Amersham, Eindhoven, The Netherlands) using a dual-headed gamma camera (Infinia Hawkeye, General Electric, Milwaukee, WI) equipped with a low-energy, high-resolution collimators (SPECT). Scans were acquired with a photopeak window centered around 159 KeV $\pm$ 10% with a 128 $\times$ 128 image matrix (zoom factor: 1.5, 40 seconds per view and 2 $\times$ 64 views). The slice thickness was 2.95 mm. Images were reconstructed using a Butterworth filter (cutoff 0.5 and Order 6). Chang's correction method was used to compensate for attenuation using a coefficient, μ, of 0.11 cm^{-1}.

Qualitative and semiquantitative analyses were performed selecting three consecutive slices with the highest striatal uptakes. Regions of interest (ROI) with fixed sizes were bilaterally drawn over the striatum (caudate nucleus and putamen) and the occipital cortex was used as the reference region. Qualitative analysis was performed by experienced physicians of nuclear medicine who was blind to the patients' clinical data. The definition as "abnormal" was ascribed to the results on the basis of the visual inspection according to previously published studies: (a) asymmetrical uptake with reduced putamen activity in one hemisphere (abnormal type 1); (b) clear symmetrical reduction of putamen uptake in both hemispheres (abnormal type 2); (c) virtual absence of uptake in both putamen and caudate nuclei on each side of the brain (abnormal type 3).[11]

^{123}I-MIBG Scintigraphy

Myocardial MIBG scintigraphy was performed at rest. A total of 111 MBq of MIGB (Amersham, Eindoven, NL) was injected intravenously in 60 seconds. Data were collected using a dual head gamma camera (Axis, Picker, Bedford, OH) at 10 minutes (early image) and 240 minutes (delayed image) after the isotope injection. Static planar imaging and regional MIBG uptake were obtained with a 128 $\times$ 128 matrix.

TABLE 1. *Demographic and clinical features in patients with mixed tremor, PD, ET, and controls*

Characteristic	Mixed tremor (n = 22)	PD (n = 20)	ET (n = 10)	CTRL (n = 18)	*P*
Age (mean ± SD)	68.95 ± 7.58	65.85 ± 6.37	68.5 ± 5.13	64.06 ± 4.84	0.076[a]
Men, n (%)	9 (40.9)	9 (45)	4 (40)	9 (50)	0.950[b]
Age at onset (mean ± SD)	58.55 ± 9.91	57.35 ± 6.07	55.50 ± 10.90	_	0.665[a]
Duration of disease (mean ± SD)	10.45 ± 7.68	8.50 ± 5.44	13.00 ± 9.91	_	0.294[a]
Familial history, n (%)	4 (18.2)	1 (5)	5 (50)	_	<0.001[b]
Clinical findings, n (%)					
Rest tremor	22 (100)	20 (100)	_	_	<0.001[b]
Postural tremor	22 (100)	_	10 (100)	_	<0.001[b]
Kinetic tremor	10 (45.5)	_	7 (70)	_	<0.001[b]
Head tremor	2 (9.1)	1 (5)	5 (50)	_	0.004[b]
Chin tremor	3 (13.6)	4 (20)	1 (10)	_	0.790[b]
Bradykinesia	15 (68.2)	20 (100)	_	_	<0.001[b]
Rigidity	19 (86.4)	20 (100)	_	_	<0.001[b]
UPDRS-ME (mean ± SD)	16.09 ± 5.24	24.20 ± 9.73	7.50 ± 1.58	_	<0.001[a]

[a]One-way ANOVA.
[b]Monte Carlo exact test.
UPDRS-ME, Unified Parkinson's Disease Rating Scale-Motor Examination.

Only planar images in thoracic anterior view were used for quantitative evaluation. ROI were drawn around the whole heart and mediastinum of the anterior image, and tracer uptake was measured within each ROI to calculate the H/M ratio. The H/M ratio from early and delayed images was evaluated in all subjects, and values were considered abnormal if they were >2 SDs below the respective control mean. Regional MIBG uptake was assessed using SPECT on the three axes displayed (short axis, vertical long axis, and horizontal long axis). Images were evaluated by an investigator who was blind to the patient's diagnoses.

Statistical Analysis

The differences in continuous variables among the study groups were assessed using one-way analysis of variance followed by unpaired *t* test corrected according to Bonferroni for multiple comparisons. Because the expected frequencies were low, Monte Carlo exact test was used to compare categorical variables among the groups.

Statistical analysis was performed with Statistical Package for Social Science Software (SPSS, version 12.0, Chicago, IL) for Windows.

RESULTS

Demographic and clinical characteristics of the patients and controls are listed in Table 1.

None of the patients had cognitive impairment, autonomic dysfunction, or brain MRI abnormalities. Combined use of DAT-SPECT and cardiac MIBG scintigraphy helped categorize the 22 mixed-tremor patients in

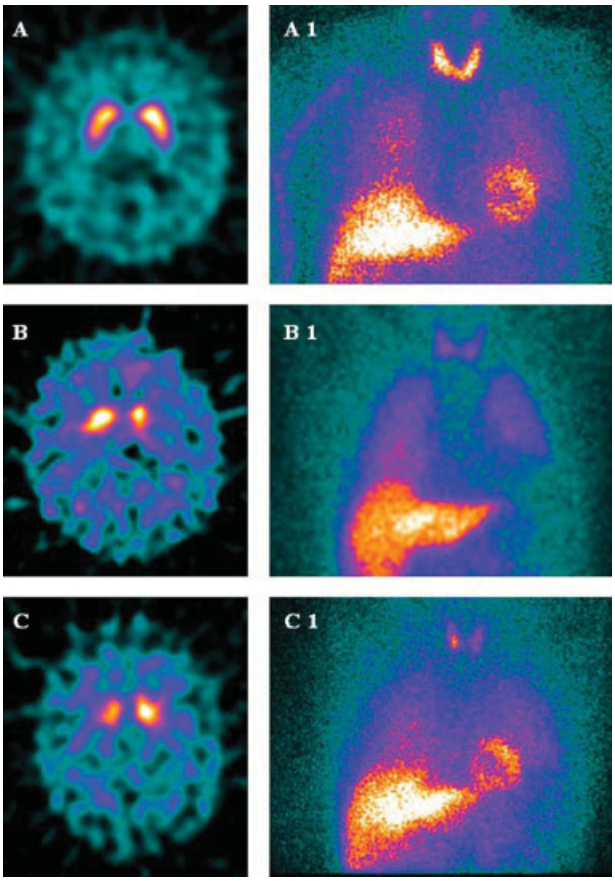

FIG. 1. Combined use of DAT-SPECT and cardiac MIBG scintigraphy in patients with mixed tremors. Normal DAT-SPECT (**A**) and normal cardiac MIBG scintigraphy (**A1**) suggesting ET (Group 1); abnormal DAT-SPECT (**B**) and abnormal cardiac MIBG scintigraphy (**B1**), indicating PD (Group 2); abnormal DAT-SPECT (**C**) and normal cardiac MIBG scintigraphy (**C1**) suggestive of parkinsonism (GROUP 3).

TABLE 2. *DAT-SPECT and cardiac MIBG scintigraphy in patients with mixed tremor*

Findings	Mixed tremor (n = 22)			
	Group 1 normal DAT-SPECT normal MIBG (n = 6)	Group 2 abnormal DAT-SPECT abnormal MIBG (n = 8)	Group 3 abnormal DAT-SPECT normal MIBG (n = 8)	*P*
Age (mean ± SD)	73.33 ± 2.97	70.25 ± 6.43	64.38 ± 9.10	0.069[a]
Male, n (%)	3 (50)	3 (37.50)	3 (37.50)	1.0[b]
Age at onset (mean ± SD)	62.17 ± 2.32	62.00 ± 7.71	52.38 ± 12.77	0.081[a]
Duration of disease (mean ± SD)	11.17 ± 4.12	8.25 ± 6.09	12.13 ± 10.88	0.603[a]
Familial history, n (%)	1 (16.7)	1 (12.5)	2 (25)	1.0[b]
Clinical findings, n (%)				
Rest tremor	6 (100)	8 (100)	8 (100)	–
Postural tremor	6 (100)	8 (100)	8 (100)	–
Kinetic tremor	3 (50)	1 (12.5)	6 (75)	0.049[b]
Head tremor	0 (0)	2 (25)	0 (0)	0.305[b]
Chin tremor	1 (16.7)	1 (12.5)	1 (12.5)	1.0[b]
Bradykinesia	3 (50)	6 (75)	6 (75)	0.612[b]
Rigidity	6 (100)	6 (75)	7 (87.5)	0.747[b]
UPDRS-ME (mean ± SD)	15.17 ± 5.23	17.38 ± 5.18	15.50 ± 5.73	0.701[a]
DAT-SPECT				
Left putamen[c]	2.61 ± 0.23	1.12 ± 0.54	1.35 ± 0.67	<0.001[a,d]
Right putamen[c]	2.59 ± 0.29	1.21 ± 0.56	1.48 ± 0.52	<0.001[a,d]
MIBG scintigraphy				
H/M ratio early image (mean ± SD)	1.79 ± 0.24	1.27 ± 0.13	1.95 ± 0.18	<0.001[a,e]
H/M ratio delayed image (mean ± SD)	1.83 ± 0.22	1.16 ± 0.11	1.90 ± 0.13	<0.001[a,f]

[a]One-way ANOVA.
[b]Monte Carlo exact test.
[c]Putamen specific to non specific (occipital area) ratio; H/M ratio = heart to mediastinum ratio.
[d]$P < 0.001$ (group 1 vs group 2 and group 1 vs group 3), unpaired *t* test with Bonferroni correction.
[e]$P < 0.001$ (group 2 vs group 1 and group 2 vs group 3), unpaired *t* test with Bonferroni correction.
[f]$P < 0.001$ (group 2 vs group 1 and group 2 vs group 3), unpaired *t* test with Bonferroni correction.
UPDRS-ME = Unified Parkinson's Disease Rating Scale-Motor Examination.

three different groups (see Fig. 1): six patients (Group 1) showed normal DAT-SPECT (right putamen: 2.59 ± 0.29; left putamen: 2.61 ± 0.23) and normal cardiac MIBG uptake (H/M ratio delayed: 1.83 ± 0.22), eight patients (Group 2) had severe decreases of tracer uptakes in both DAT-SPECT (right putamen: 1.21 ± 0.56; left putamen: 1.12 ± 0.54) and cardiac MIBG scintigraphies (H/M ratio delayed: 1.16 ± 0.11), and eight patients (Group 3) had decreased striatal DAT uptakes (right putamen: 1.48 ± 0.52; left putamen: 1.35 ± 0.67) but normal cardiac MIBG scintigraphy (H/M ratio delayed: 1.90 ± 0.13) (Table 2). Five of eight patients in Group 2 and four of eight patients in Group 3 had abnormal DAT-SPECT type I, whereas all other patients in both Group 2 and Group 3 had abnormal DAT-SPECT type II. Furthermore, in Figure 2, the box plots separately depicting DAT-SPECT binding and cardiac MIBG uptake values in the three different groups of mixed-tremor and in PD, ET, and control subjects are showed.

There were no clinical differences among these mixed-tremor groups (Table 2). All patients with damaged dopaminergic striatal system were followed-up for 12.66 ± 9.07 months (Group 2: 13.37 ± 8.87 months, mean ± SD; Group 3: 11.87 ± 7.73 months). All patients in Group 2 displayed a good chronic levodopa responsiveness (baseline UPDRS-ME: 17.38 ± 5.18; follow-up UPDRS-ME: 11 ± 2.67), whereas in Group 3, six of eight patients had a poor chronic levodopa responsiveness (baseline UPDRS-ME: 15.50 ± 5.73; follow-up UPDRS-ME: 14.75 ± 5.72).

Demographics and clinical data of the probable PD and probable ET and of the control subjects are shown in Table 1. DAT–SPECT and MIBG scintigraphies were both markedly abnormal in probable PD (right putamen: 1.12 ± 0.30; left putamen: 1.14 ± 0.20; H/M ratio delayed: 1.10 ± 0.09), whereas they were both normal in probable ET (right putamen: 2.38 ± 0.2; left putamen: 2.36 ± 0.3; H/M ratio delayed: 1.98 ± 0.08) and control subjects (right putamen: 2.45 ± 0.2; left putamen: 2.42 ± 0.2; H/M ratio delayed: 1.99 ± 0.18).

DISCUSSION

Our study demonstrates that mixed tremor is an heterogeneous disorder and that combined use of DAT-

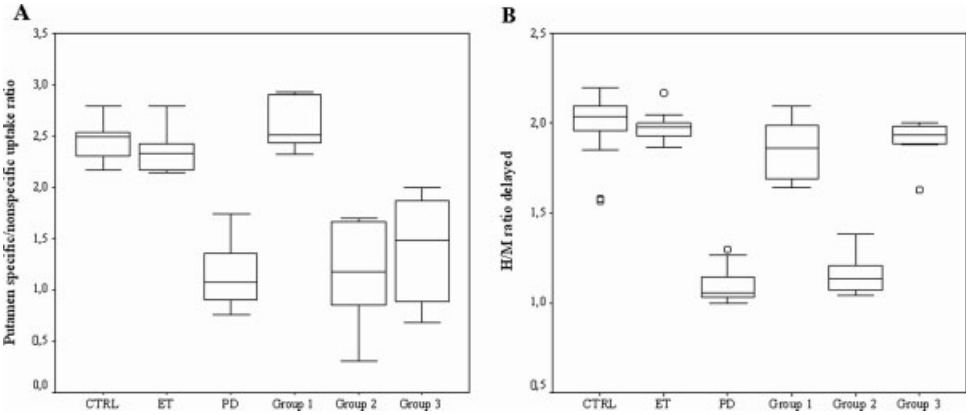

FIG. 2. Box-plot of DAT-SPECT (**A**) and cardiac MIBG scintigraphy (**B**) values in control subjects, patients with ET, PD, and mixed tremor (Group 1, Group 2, and Group 3). DAT-SPECT values are reported as mean putamen specific to nonspecific (occipital area) uptake ratio. Cardiac MIBG scintigraphy values are reported as heart/mediastinum ratio in delayed image (H/M ratio delayed).

SPECT and cardiac MIBG scintigraphy can help differentiate patients with tremor disorders clinically undistinguishable. Indeed, by using these imaging tools, in our study population, we were able to identify six patients with ET, eight with PD, and the remaining eight with parkinsonism.

Mixed tremor is a combination of postural and rest tremor that can be found either in ET or in PD.

Predominant mixed-tremor phenotype can be the sole clinical manifestation (isolated mixed tremors) or may occur in addition to mild extrapyramidal features (mixed tremor plus). At the present time, it is not well established whether the presence of additional extrapyramidal features in these patients may coexist with an intact nigrostriatal pathway, as it has been reported in a proportion of patients with isolated mixed tremors.[12]

DAT-SPECT is a reliable means to detect the degeneration of the nigrostriatal dopaminergic system both in PD and parkinsonism, but it may also be of value in patients with isolated tremors in whom clinical diagnosis may be difficult. Indeed, reduced putaminal DAT binding has been reported in patients with isolated postural tremor,[12,13] monosymptomatic rest tremor,[13,14] or a combination of the two,[12,15–17] suggesting that these patients might have PD at a presymptomatic stage.

In contrast, a study focused only on mixed tremor associated with mild extrapyramidal features.[16] In this study, the authors investigated 23 patients with postural and rest tremor associated with cogwheel rigidity and reduced arm swing and demonstrated that about half of them showed normal putamen^{18}F-dopa uptake, suggesting that the presence of additional extrapyramidal features was not a useful predictor of PD.[16] In agreement with this observation, our study shows that a proportion (6 of 22; 27%) of the patients with mixed tremor and additional mild extrapyramidal features had preserved nigrostriatal dopaminergic system, a finding typically observed in ET. The occurrence of extrapyramidal signs in patients with a diagnosis of ET is not uncommon, and patients who satisfy the criteria of classical ET but exhibit neurologic signs such as hypomimia, decreased arm swing, or mild bradykinesia are currently classified as an indeterminate tremor syndrome.[8] Our patients could be included in this subtype of ET even if the hypothesis of a SWEDD tremor predominant parkinsonian syndrome cannot be excluded. However, the long duration of the disease (11.2 $\pm$ 4.1 years) makes this latter hypothesis unlikely. Follow-up studies to evaluate the possible development of PD in patients with mixed tremor with additional extrapyramidal features and normal DAT-SPECT are warranted.

In our study, the remaining 16 of the 22 mixed-tremor patients showed damage to the nigrostriatal system, suggesting a parkinsonian disorder. DAT-SPECT, however, does not allow to differentiate among patients with mixed tremors those with PD from those with parkinsonian syndromes.

Reduced MIBG uptake has been demonstrated in PD either in the early or in the late phases of the disease or in the absence of autonomic dysfunction, a finding that is related to the presence of Lewy body pathology in cardiac sympathetic nerve endings.[18,19] In contrast, normal cardiac MIBG uptake has been reported in patients with ET[20] and patients with parkinsonism such as multiple system atrophy (MSA),[6,21] progressive supranuclear palsy (PSP),[6] and corticobasal degeneration (CBD),[22] indicating that MIBG scintigraphy may help distinguish patients with idiopathic PD from those with ET or those with atypical parkinsonian syndromes.

In our study, of the 16 mixed-tremor patients with abnormal DAT-SPECT, eight had reduced cardiac tracer uptakes, a finding strongly suggestive of PD, whereas the remaining eight had normal tracer uptake indicating a parkinsonism. These eight patients with PD had a tremor-predominant phenotype characterized by the presence of resting and postural tremor, with other signs of PD being present but very mild also after a long duration of disease. The tremor-predominant PD is a clinical subtype with a unique clinical course different from that of typical PD. Despite clinical differences between typical PD and tremor-predominant PD, myocardial MIBG scintigraphy has been reported to be impaired also in this latter form of PD[23] thus supporting the hypothesis that both clinical phenotypes are linked to a Lewy body pathology.

Because of their mild disability, patients with tremor-predominant PD usually are not compliant to the dopaminergic therapy. Indeed, our tremor-predominant PD patients had a history of dopaminergic treatment taken at low dosage, discontinuously, and for short periods of time, making uncertain levodopa responsiveness. When these patients were treated with chronic levodopa therapy, for about a year, they showed good drug responsiveness, thus confirming the diagnosis of PD.

The remaining eight patients with mixed tremor and abnormal DAT-SPECT had normal myocardial MIBG uptake indicating the integrity of cardiac nerve endings, thus suggesting a parkinsonism. The finding of parkinsonism in this group of patients with a relatively long duration of the disease, and a clinical picture of a tremor-predominant phenotype is quite surprising. The majority (six of eight) of these patients showed poor chronic levodopa responsiveness, a finding in favor of a parkinsonian disorder different from PD. Which type of parkinsonism these patients may have is still unknown. None of the patient fulfilled clinical established criteria for PSP,[24] MSA,[25] and CBD,[26] and MRI images were normal in all cases, thus making the diagnosis of atypical parkinsonian syndrome unlikely.

Diagnoses other than parkinsonism could be considered in Group 3, because the techniques used in the current study may be inaccurate in some patients with early-phase PD[27] or ET.[28] However, this does not seem to be our case because all these patients but one had a long duration of the disease (rang, 4–32 years), and DAT-SPECT values were markedly abnormal similar to those typically occurring in PD.

Recently, some authors reported 16 patients affected by benign tremulous parkinsonism, a distinct clinical entity characterized by a predominance of mixed tremor (resting and postural in almost all patients but also kinetic tremor in some cases), with mild bradykinesia, rigidity, and a poor levodopa response.[29] A family history of tremor and/or PD was also reported in a significant number of patients (10 of 16 or 63%) with this disorder. Although the neuropathology of benign tremulous parkinsonism is lacking, a previous striatal dopaminergic imaging study[16] has demonstrated reduced putamen tracer uptake in patients with this phenotype. Our patients with abnormal DAT-SPECT and normal cardiac MIBG uptake all showed a clinical picture strongly resembling that described in benign tremulous parkinsonism. Indeed, they showed a tremor predominant phenotype characterized by a mixture of resting and postural tremors with an additional kinetic tremor in 75% of the cases. Bradykinesia and rigidity were present in the majority of patients (75% and 87.5%, respectively) and poor chronic levodopa responsiveness was detected in 75% of the cases. In our series, a family history of PD and/or tremor was present in only two (25%) of eight patients, a percentage lower than that previously found in benign tremulous patients,[27] but the small sample reported here (eight patients) may account for this discrepancy.

There are some limitations to this study. We lack pathologic data, and we do not know whether our patients with mixed tremor and normal MIBG scintigraphy lacked Lewy body pathology in the brain and sympathetic nerve endings. However, at the present time no pathologic data exist in patients with benign tremulous parkinsonism.

Our study emphasizes the importance of a combined use of both DAT-SPECT and cardiac MIBG scintigraphy to refine the diagnosis in patients with mixed tremors and mild extrapyramidal features. Additional studies in a larger cohort of patients are warranted.

Authors' Roles: FN: Research Project (Organization and Execution); Statistical Analysis (Review and Critique); Manuscript (Writing of the first draft and Review and Critique). GA: Research Project (Execution); Statistical Analysis (Design and Review and Critique); Manuscript (Review and Critique). AB: Research Project (Execution); Manuscript (Review and Critique). GLC: Research Project (Execution); Manuscript (Review and Critique). MS: Research Project (Execution); Manuscript (Review and Critique). GN: Research Project (Execution); Manuscript (Review and Critique). DM: Research Project (Execution); Statistical Analysis (Review and Critique). MM: Research Project (Execution); Manuscript (Review and Critique). SP: Research Project (Execution); Manuscript (Review and Critique). LG: Research Project (Execution); Manuscript (Review and Critique). AR: Research Project (Execution); Manuscript (Review and Critique). GT: Research Project (Execution). FC: Statistical Analysis (Execution); Manuscript (Review and Critique). AQ: Research Project (Conception and Organization); Statistical Analysis (Design and Review and Critique); Manuscript (Review and Critique).

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