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Loss of Dopamine-D2 Receptor Binding Sites in Parkinsonian Plus Syndromes

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This study analyzed temporal changes of striatal dopamine-D2 receptor binding during the course of different extrapyramidal movement disorders using ^{123}I-iodobenzamide (IBZM) SPECT. **Methods:** Eighteen patients (9 with Parkinson's disease, 9 with parkinsonian plus syndrome) were followed for 11–53 mo. Dopamine-D2 receptor binding was assessed using ^{123}I-IBZM SPECT at the beginning and at the end of the follow-up period. SPECT data were acquired 120 min postinjection of 3–5 mCi ^{123}I-IBZM. A semiautomated algorithm was applied to the raw data for semiquantitative evaluation of regional cerebral receptor binding. **Results:** Intraobserver ($r = 0.992$) and interobserver ($r = 0.930$) variance was low for the semiautomated interpretation of the SPECT examination of the dopaminergic D2 receptor binding, reflecting a highly reproducible SPECT algorithm. Mean specific dopamine-D2 receptor binding was lower in patients with parkinsonian plus syndrome compared to patients with Parkinson's disease on the initial ($p < 0.001$) as well as the follow-up study ($p < 0.001$). In patients with Parkinson's disease, we observed an unaffected receptor binding compared to a reduced binding of radiotracer in patients with parkinsonian plus syndrome during the course of the disease ($p < 0.001$). **Conclusion:** During the follow-up, patients with Parkinson's disease showed a constant dopamine-D2 receptor binding. In contrast, patients with parkinsonian plus syndrome revealed a decline of the binding of dopamine-D2 receptor. These findings are in agreement with histopathological data that demonstrated a preserved dopamine-D2 receptor status in patients with Parkinson's disease and a decline of the dopamine-D2 receptors in patients with parkinsonian plus syndrome. SPECT examinations using ^{123}I-IBZM are useful for assessing dynamic changes of dopamine-D2 receptors in extrapyramidal movement disorders. Semiquantitative SPECT evaluations may provide valuable information for clinical management and prognosis of the patient with extrapyramidal movement disorders.

Key Words: Parkinson's disease; parkinsonian plus syndromes; iodine-123-iodobenzamide; SPECT

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Parkinson's disease, multiple system atrophy and progressive supranuclear palsy are pathologic conditions that involve the extrapyramidal control of voluntary and involuntary movement. It is well known that these conditions are difficult to discriminate by clinical means although the underlying pathology is distinct. In fact, even in specialized centers, in up to 30% of the cases clinically diagnosed as Parkinson's disease, postmortem examination revealed changes consistent with multiple system atrophy or other parkinsonian disorders (*1,2*). Although some encouraging results have been published recently using MRI (*3,4*), structural neuroimaging fails to identify, with sufficiently high specificity, these different extrapyramidal disorders. Since the prognosis varies among these disorders, being rather poor in patients with parkinsonian plus syndrome compared to patients with Parkinson's disease, active diagnostic information is use-

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TABLE 1
Demographic and Clinical Data

Patient no.	Age (yr)	Gender	Dx	H&Y	Duration	de-novo	Medication 1*	Medication 2†
1	48	F	PD	1/1	1	Yes	None	LD 500 mg/day D 250 mg/day P 1.25 mg/day
2	80	M	PD	3/4	8	No	LD 375 mg/day D 250 mg/day	LD 475 mg/day
3	42	F	PD	2/4	6	No	LD 375 mg/day D 62.5 mg/day	LD 625 mg/day
4	59	M	PD	2/2	2	No	LD 750 mg/day	LD 875 mg/day
5	74	M	PD	3/3	6	No	LD 625 mg/day	LD 575 mg/day
6	53	M	PD	1/1	4	Yes	None	LD 875 mg/day
7	72	M	PD	2/2	2	Yes	None	LD 375 mg/day D 125 mg/day
8	51	M	PD	1/1	4	No	n.a.	LD 1000 mg/day
9	48	F	PD	2/4	10	No	AM 3.7 mg/hr	AM 3.5 mg/hr
10	55	F	SND	3/4	5	No	LD 1000 mg/day	LD 800 mg/day P 2 mg/day
11	61	F	SND	2/4	5	No	n.a.	LD 750 mg/day
12	53	F	PSP	3/5	4	No	LD 800 mg/day	LD 625 mg/day
13	75	F	OPCA	2/2	4	No	LD 450 mg/day	LD 600 mg/day
14	21	M	OPCA	3/4	5	No	LD 400 mg/day D 250 mg/day	LD 100 mg/day P 2.5 mg/day
15	67	F	PSP	2/4	2	No	n.a.	LD 800 mg/day
16	62	M	PSP	3/5	11	No	LD 1000 mg/day D 250 mg/day B 17.5 mg/day	LD 1200 mg/day D 125 mg/day
17	58	M	SND	2/3	9	Yes	None	LD 1000 mg/day D 250 mg/day P 3 mg/day
18	52	M	PSP	2/3	2	Yes	None	LD 750 mg D 250 mg/day

*Medications prescribed at initial SPECT scan.
†Medications prescribed at follow-up SPECT scan.
PD = Parkinson's disease; SND = multisystem atrophy typ striato-nigral degeneration; PSP = progressive supranuclear palsy; OPCA = multisystem atrophy typ olivo-ponto-cerebellar atrophy; H&Y = clinical grading according to the Hoehn and Yahr classification (initial/follow-up examination); duration = time since initial diagnosis (years); de-novo = no prior anti-Parkinson medication; LD = L-dopa; D = deprenyl; P = pergolide; AM = apomorphin; n.a. = data not available.

ful to plan future medical as well as family needs (*5*). In addition, ^{123}I-iodobenzamide (IBZM) SPECT could be used to screen and to provide prognostic information and even genetic counseling to individuals and high-risk groups.

The striatal dopamine-D2 receptor plays a key role in transmitting nigral stimuli to the neostriatum. The cerebral distribution of these receptors in patients with extrapyramidal movement disorders has been studied extensively by numerous authors using PET or SPECT (*6–9*). However, there is a lack of information concerning the longitudinal changes of the striatal dopamine-D2 receptor binding during the time course of extrapyramidal movement disorders. The goal of our study was to assess temporal changes of striatal dopamine-D2 receptor status using ^{123}I-IBZM SPECT in patients with different parkinsonian disorders during a follow-up period.

MATERIALS AND METHODS

Patients

Nine patients with Parkinson's disease (3 women, 6 men; age range 42–80 yr; mean age 58.6 yr) were studied. All patients met the criteria for Parkinson's disease according to the United Kingdom brain bank diagnostic criteria (*10,11*). Nine patients (6 women, 3 men; age range 21–75 yr; mean age 56 yr) met the criteria for parkinsonian plus syndrome (multiple system atrophy, n = 5; progressive supranuclear palsy, n = 4). The clinical diagnosis was assessed according to the criteria proposed by Quinn (*1*) for multiple system atrophy and by Steele et al. (*12*) for progressive supranuclear palsy. There was no statistically significant difference in age between the two groups ($p > 0.5$).

Disease duration from the time of first symptoms to the first SPECT study was 1–10 yr (mean = 4.8 yr) for patients with Parkinson's disease and 2–11 yr (mean = 5.2 yr) for parkinsonian plus syndrome patients. Clinical grading was accomplished according to Hoehn and Yahr (*13*) criteria and scores were determined to be between 1 and 5. All but three Parkinson's disease and two parkinsonian plus syndrome patients (Table 1) received anti-Parkinson medication for at least 2 yr before the initial SPECT study. Medication doses prescribed at each scanning session and demographic data are listed in Table 1. For all patients, anti-Parkinson medication was withdrawn at least 12 hr before each SPECT study. None of the patients presented with dementia.

Patients were selected to obtain a study population of individuals with clinically typical presentation of either Parkinson's disease or parkinsonian plus syndrome with symmetric expression of symptoms. Patients with uncertain diagnoses were excluded from our analysis.

All patients were referred to us by the outpatient clinic of the neurologic department of our institution for assessment of the striatal dopamine-D2 receptor status. Every patient who was studied gave written informed consent before each SPECT study.

SPECT Imaging

An oral dose of 300 mg sodium perchlorate was given to each patient 30 min before the study to protect the thyroid gland from uptake of free iodine. SPECT acquisition (360° rotation, step-and-shoot mode) was started 120 min after intravenous injection of a bolus of 111–185 MBq (3–5 mCi) sterile, pyrogen-free ^{123}I-IBZM. The imaging parameters for dopamine-D2 receptor SPECT were described previously (*14*). For both initial and follow-up studies, data were acquired by the same gamma camera system with a low-energy medium-resolution, parallel-whole collimator single-head gamma camera (Apex 409 with LEAP APC-3, Elscint, Wiesbaden, Germany) connected to a dedicated computer system and reconstructed using a modified Hann filter for backprojection. The same four-step algorithm (MSCBREOB4X, Medisoft, Witten, Germany) that was described previously was applied to the acquired data (*14*).

Using ROI analysis, dopamine-D2 receptor binding within the neostriatum was assessed by calculating ratios between the tracer uptake in the neostriatum (NS) and, as a control region, the cerebellum (CB). This ratio (NS/CB) has been shown to correlate directly with the actual dopamine-D2 receptor density as measured by ^{11}C-raclopride PET (*15*). The size of the ROI measured approximately 9 ml. Whole-body radiation exposure was calculated as 0.6 mSv/mCi based on the biodistribution ascertained by Kung et al. (*16*) and ICRP 26 (*17*).

Each patient was studied twice under identical study conditions. The mean time interval between the two examinations was 39.6 mo (range = 26–53 mo) for Parkinson's disease patients and 25.8 mo (range = 11–41 mo) for parkinsonian plus syndrome patients.

Repositioning was assured by using identical anatomical landmarks and a specially-designed head holder. The reconstruction algorithm allows adjustment for tilted head position in all three planes to obtain identically-orientated SPECT images from all studies (*14*).

Variability and Reproducibility

Crucial for the data value obtained in follow-up studies is the variability and, therefore, the reproducibility of the results. Since single-head gamma camera study image quality is limited due to the lower counting rate, compared to more advanced systems, a special concern was assessing interobserver and intraobserver variability of the reconstruction and evaluation algorithm before looking at follow-up data.

The data of eight patients (three with a high striatal binding, one with a very low striatal binding and four with an intermedium striatal binding of ^{123}I-IBZM) were anonymized and duplicated seven times to obtain 56 datasets. These were mixed and presented to an experienced reader blinded to any clinical information at the time of the reading. To assess the intraobserver variability mean values (x), s.d. and the coefficient of variance (VC) were calculated using a two-way analysis of variance (ANOVA).

To assess interobserver variability, the datasets of 10 patients with Parkinson's disease and 9 with parkinsonian plus syndrome were anonymized and given to two independent readers for reconstruction and evaluation. Both readers, one of them experienced in the field and one a first-year resident, were blinded to any clinical information at the time of the reading. Absolute and relative differences between individual results (D and D%) were calculated according to:

$$\text{Absolute difference: } D = NS/CB_{(A)} - NS/CB_{(B)}. \quad \text{Eq. 1}$$

$$\text{Relative difference: } D\% = \frac{NS/CB_{(A)} - NS/CB_{(B)}}{NS/CB_{(A)} + NS/CB_{(B)}} \times 2, \quad \text{Eq. 2}$$

$NS/CB_{(A)}$ = results obtained by Reader A.

TABLE 2
Results

Patient no.	IBZM*	IBZM†	Interval‡	$D_{NS/CB}$§	$\Delta_{NS/CB}$¶
1	1.74	1.80	46	0.060	0.001
2	1.67	1.76	47	0.090	0.002
3	1.55	1.78	53	0.230	0.003
4	1.69	1.76	27	0.070	0.002
5	1.75	1.73	34	−0.020	0.000
6	1.87	1.92	42	0.050	0.001
7	1.73	1.71	45	−0.020	0.000
8	1.80	1.80	26	0.000	0.000
9	1.85	1.89	36	0.004	0.001
10	1.61	1.51	18	−0.100	−0.003
11	1.63	1.50	11	−0.130	−0.007
12	1.66	1.52	23	−0.140	−0.004
13	1.46	1.56	18	0.100	0.004
14	1.04	1.13	30	0.090	0.003
15	1.57	1.12	31	−0.450	−0.009
16	1.52	1.45	32	−0.070	−0.001
17	1.49	1.44	41	−0.050	−0.001
18	1.44	1.35	28	−0.090	−0.002

*Individual results of the initial IBZM SPECT study.
†Individual results of the follow-up SPECT study.
‡Interval between SPECT studies in months.
§$D_{NS/CB}$ = absolute difference according to Equation 5.
¶$\Delta_{NS/CB}$ = slopes according to Equation 6.

$NS/CB_{(B)}$ = results obtained by Reader B.

The level of agreement between the two observers, indicating the range within which most of their disagreements occur, was calculated. In addition, the 95% range of agreement, which is based on the mean difference (d) and the s.d. of these differences [SD(d)] can be calculated using:

$$95\% - \text{range of agreement} = (d) \pm 2 \times \text{s.d. } (d), \quad \text{Eq. 3}$$

where (d) = mean difference between Reader A and Reader B and s.d. (d) = standard deviation of (d).

Estimating the true value of (d) between the two observers for a 95% confidence interval, based on the sample studied, is represented by the s.e.m. difference [SE(d)]. The 95% confidence interval for (d) can be calculated using:

$$95\% - \text{confidence interval} = (d) \pm 2 \times \text{s.e. } (d), \quad \text{Eq. 4}$$

where (d) = mean difference between Reader A and Reader Q and s.e. (d) = standard error of (d).

If zero lies within this given interval, it is concluded that there is no significant bias between the two observers (*18*).

The results were correlated with the reader's experience, being considered limited for Reader B (first-year resident) compared to Reader A (7 yr neuroimaging experience). For all calculations, statistical significance was assumed at a p value below 0.05.

RESULTS

The specific dopamine-D2 receptor binding of ^{123}I-IBZM in the striatum, compared to the reference region of nondopaminergic brain tissue (cerebellum), is expressed as a ratio (NS/CB) and listed for each patient in Table 2.

Intraobserver Variance and Reproducibility

The s.d. of repeated measurements of striatal uptake of ^{123}I-IBZM ranged from 0.015–0.074 for the 8 patients. The VC

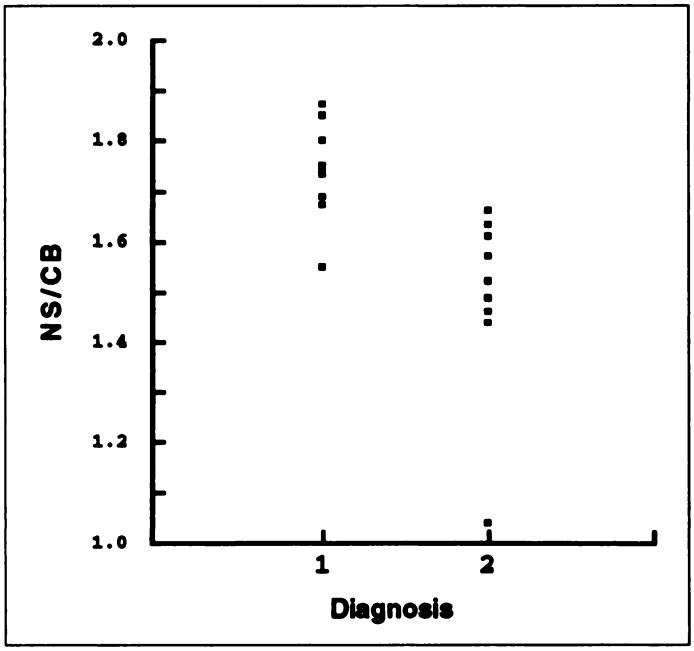

FIGURE 1. Specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors (NS/CB) in patients with Parkinson's disease (Diagnosis 1) compared with patients with parkinsonian plus syndrome (Diagnosis 2). Individual data points of initial SPECT study are included. Difference of mean values is statistically significant ($p < 0.001$, Mann-Whitney test).

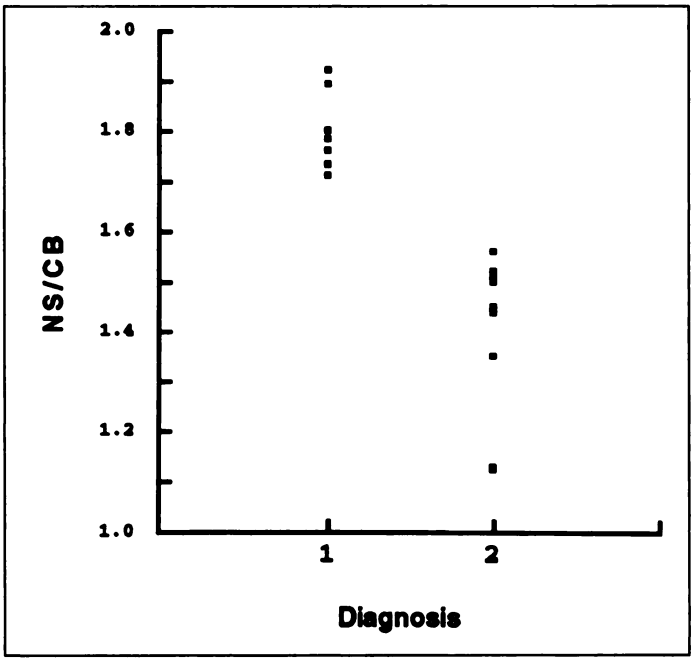

FIGURE 2. Specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors (NS/CB) in patients with Parkinson's disease (Diagnosis 1) compared with patients with parkinsonian plus syndrome (Diagnosis 2). Individual data points of the follow-up SPECT study are included. Difference of mean values is statistically significant ($p < 0.001$, Mann-Whitney test).

ranged from 0.009–0.044 (0.9%–4.4%) with a mean of VCx = 0.023 (2.3%; s.d. = 0.9%). The two-way ANOVA revealed a correlation coefficient r = 0.992 ($p < 0.001$) indicating a low intraobserver variance and, therefore, a high reproducibility. There was no correlation between the actual striatal tracer uptake and the variance of the results (r = 0.001, correlation analysis).

Interobserver Variance and Reproducibility

The absolute (D) and relative (D%) differences were calculated between the two readers, A and B. The mean values were $\overline{X}_D$ = 0.001 (range = −0.14–0.17; s.d. = 0.08) and $\overline{X}_{D\%}$ = 4.3% (range = 0%–11.3%; s.d. = 3.1%), respectively. The 95% range of agreement, $D_{95\%SD}$, was between −0.15 and 0.17, while the 95% confidence interval, $D_{95\%SE}$, was between −0.025 and 0.027. The analysis of the correlation between the results of Readers A and B revealed r = 0.93 ($p < 0.001$). Both results underline the low interobserver variance and the high interobserver reproducibility of the results. There was no statistically significant influence of the level of professional experience on the results of this analysis ($p > 0.05$; Mann-Whitney test).

Semiquantitative Analysis of Initial Iodine-123-IBZM Study

Mean specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors in patients with Parkinson's disease was NS/CB = 1.74 (range = 1.55–1.87; s.d. = 0.10) compared to NS/CB = 1.49 (range 1.04–1.66; s.d. = 0.18) in patients with parkinsonian plus syndrome. Statistical analysis revealed a significant difference between the two populations (p = 0.001, Mann-Whitney test), however, a significant overlap between both study groups was found (Fig. 1). For individual data, see Table 2.

Semiquantitative Analysis of Follow-Up Iodine-123-IBZM Study

In all patients, follow-up clinical assessment confirmed initial diagnoses of either Parkinson's disease or parkinsonian plus syndrome. Clinical diagnoses based on assessing the recognized clinical criteria also was supported by positive responsiveness to medication for the Parkinson's disease group and poor benefit from dopaminergic medication for the parkinsonian plus syndrome group.

On follow-up (time interval 11–53 mo), mean NS/CB in patients with parkinsonian plus syndrome dropped to NS/CB = 1.40 (range = 1.12–1.56; s.d. = 0.14) compared to NS/CB = 1.79 (range = 1.71–1.92; s.d.= 0.066) in patients with Parkinson's disease now showing no overlap between the two populations (Fig. 2) ($p < 0.0001$, Mann-Whitney test). In Parkinson's disease patients, no statistically significant difference was found between the Hoehn and Yahr grading at the time of the initial SPECT (median: Hoehn and Yahr = 2) study compared to the follow-up SPECT study (median: Hoehn and Yahr = 2) (p = 0.18, Wilcoxon-test). In PPS patients, the initial median measured Hoehn and Yahr = 2 versus Hoehn and Yahr = 4 on the day of follow-up (p = 0.01, Wilcoxon). For individual data, see Table 1.

Analysis of Follow-Up Data

Longitudinal changes of the specific striatal binding of ^{123}I-IBZM can be expressed as absolute changes of the NS/CB ratio (DNS/CB) during the follow-up period according to:

$$D\,(NS/CB) = NS/CB_{(1)} - NS/CB_{(2)}, \qquad \text{Eq. 5}$$

$NS/CB_{(1)}$ = initial NS/CB ratio.
$NS/CB_{(2)}$ = follow-up NS/CB ratio.

We found mean D (NS/CB) to measure −0.056 (s.d. = 0.076) in Parkinson's disease patients compared to 0.093 (s.d. = 0.160) in parkinsonian plus syndrome patients ($p < 0.0001$, Mann-Whitney test) (Fig. 3).

Since the follow-up period varied considerably among our study group, we compared the changes of striatal binding of ^{123}I-IBZM over time and, since only two data points were available for each patient, a linear model of evolution was assumed and the slopes of the individual time courses ($\Delta_{NS/CB}$) were calculated according to:

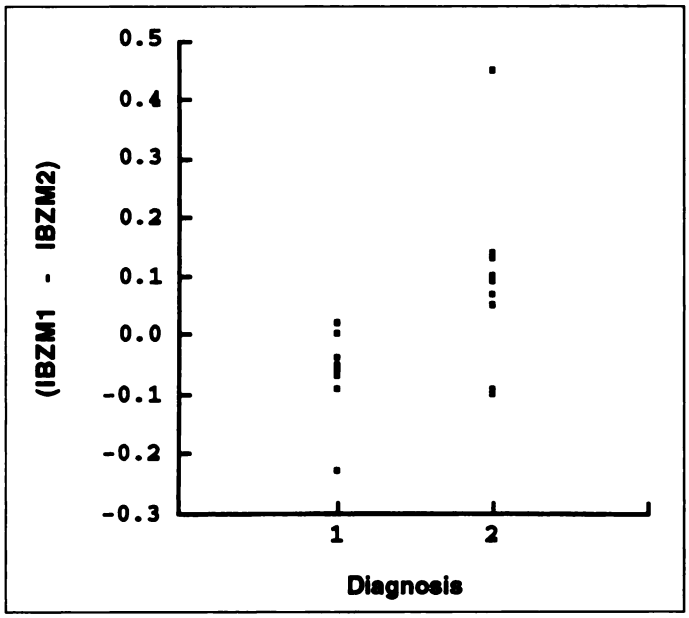

FIGURE 3. Comparison of absolute differences of specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors (DNS/CB) in patients with Parkinson's disease (Diagnosis 1) or parkinsonian plus syndrome (Diagnosis 2) according to Equation 5. Difference of mean values is statistically significant ($p < 0.001$, Mann-Whitney test).

$$\Delta NS/CB = \frac{(NS/CB_{(2)} - NS/CB_{(1)})}{NS/CB_{(1)} \times t}, \qquad \text{Eq. 6}$$

t = time interval between SPECT examinations (month).

We compared these slopes between the two groups by a nonparametric test (Mann-Whitney test). In patients with parkinsonian plus syndrome, all but two showed a negative slope of the binding curve of ^{123}I-IBZM. The mean slope measured $\Delta_{NS/CB} = -2.4 \times 10^{-3}$ per month (s.d. $= 4 \times 10^{-3}$), (Fig. 4). Patients with Parkinson's disease had a rather constant or even

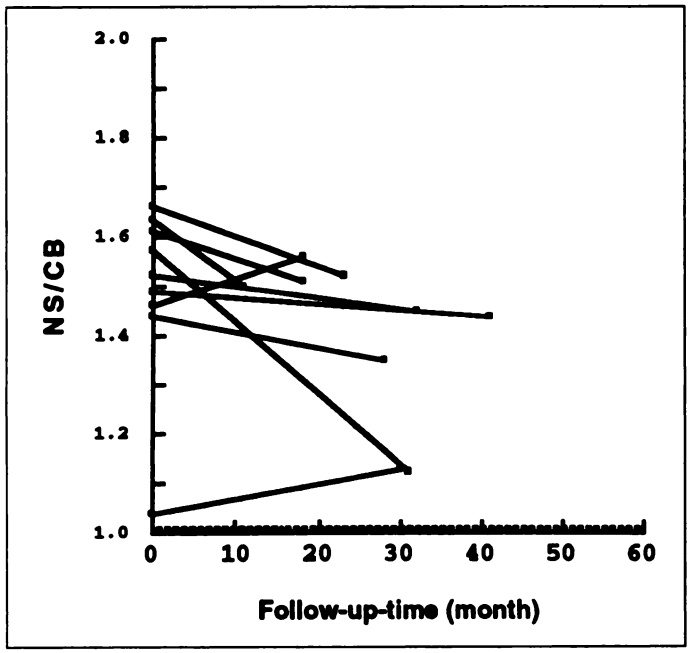

FIGURE 4. Longitudinal assessment of specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors (NS/CB) in patients with parkinsonian plus syndrome over time of follow-up. Individual datasets of both SPECT studies are included.

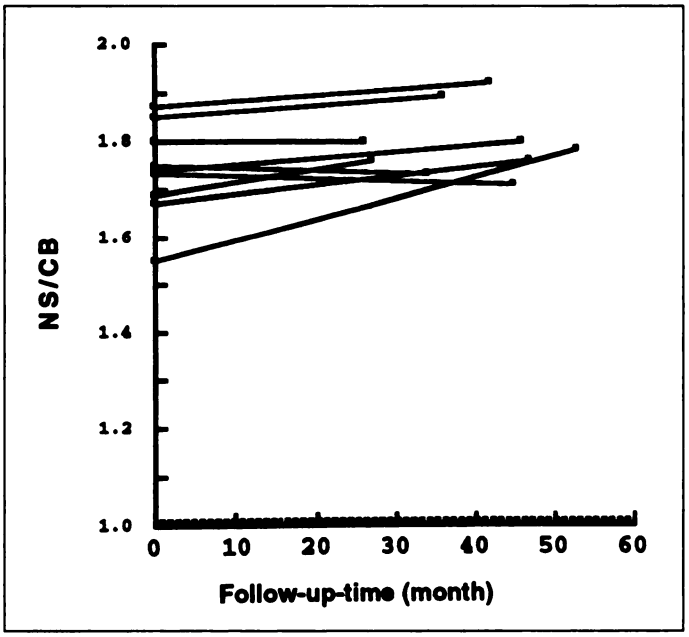

FIGURE 5. Longitudinal assessment of specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors (NS/CB) in patients with Parkinson's disease over time of follow-up. Individual datasets of both SPECT studies are included.

increasing binding curve of ^{123}I-IBZM over time with a mean slope of $\Delta_{NS/CB} = 0.9 \times 10^{-3}$ per month (s.d. $= 1 \times 10^{-3}$), (Fig. 5).

Statistical analysis revealed a significant difference between the two groups regarding the mean slope expressing dynamic changes of the striatal binding of ^{123}I-IBZM ($p < 0.001$, Mann-Whitney test, Fig. 6).

No statistically significant correlation was found between the follow-up duration and the $\Delta_{NS/CB}$-value or between the time elapsed between scans and clinical changes of the individual patient in either group. Individual values for these variables are reported in Table 2.

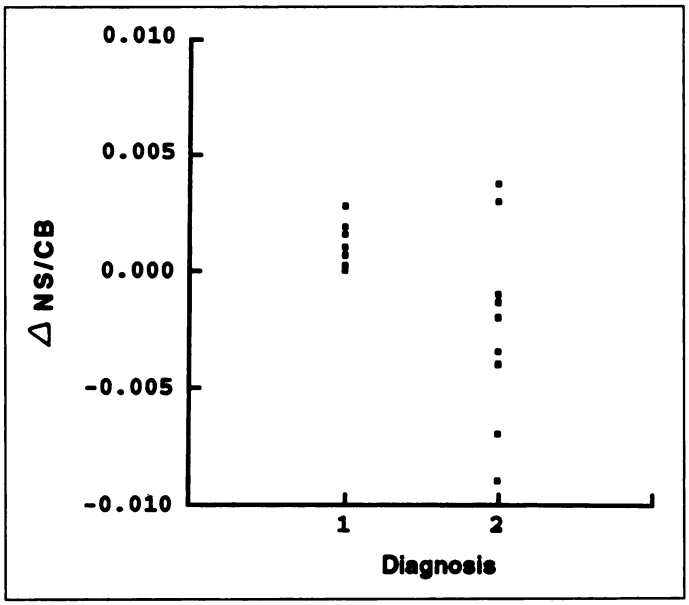

FIGURE 6. Comparison of slopes of individual time courses of specific striatal ^{123}I-IBZM binding to dopamine-D2 receptors ($\Delta_{NS/CB}$) in patients with Parkinson's disease (Diagnosis 1) or parkinsonian plus syndrome (Diagnosis 2) according to Equation 6. Difference of mean values is statistically significant ($p < 0.001$, Mann-Whitney test).

DISCUSSION

In keeping with our previous studies, we found SPECT examinations with ^{123}I-IBZM suitable for discriminating between patients with Parkinson's disease and parkinsonian plus syndrome by looking at the striatal uptake of this dopamine-D2 receptor ligand (*8,19*). However, a substantial overlap of the results created a significant differential diagnostic problem. Some patients with clinically typical Parkinson's disease had unexpectedly low striatal binding, whereas parkinsonian plus syndrome patients had relatively high uptake of ^{123}I-IBZM within the striatum (*8*).

Previous estimates of the progression rate of neurodegenerative disorders have been derived mainly from pathologic studies with mostly inherent selection bias. In a recent study, Vingerhoets et al. (*20*) found that dopaminergic function, in terms of presynaptic dopamine synthesis, declines more rapidly in patients with Parkinson's disease than in normal aging.

In our retrospective longitudinal study, however, we found characteristic temporal changes of postsynaptic striatal binding of ^{123}I-IBZM using SPECT. Patients with Parkinson's disease maintained a rather constant receptor binding over time. Even those patients with initially relative low receptor binding did not show a significant decrease of the NS/CB ratio over time. This is consistent with the stable clinical symptoms, reflected by a constant Hoehn and Yahr grading in 6 of 9 patients, while 3 of 9 patients were classified as worse on follow-up clinical examination.

Patients with parkinsonian plus syndrome are characterized by a gradual loss of striatal binding of ^{123}I-IBZM during the course of the disease. This gradual loss of residual motor function in patients with parkinsonian plus syndrome is accompanied by a worsened Hoehn and Yahr score on follow-up in 8 of 9 patients, while 1 of 9 patients had constant Hoehn and Yahr grading (Table 1).

On the follow-up study, we were able to discriminate even more precisely between the two groups and a cutoff value of the NS/CB ratio could be defined. The use of ^{123}I-IBZM SPECT differentiation is easier in more advanced stages of the disease than it is in earlier stages. From the clinical point of view, these results limit the value of the performance of initial SPECT studies when symptoms are equivocal.

A future application could be the evaluation of neuroprotective treatment modalities since the clinical assessment of neuroprotection cannot be assessed accurately (*21*). A potential neuroprotective treatment could be monitored, therefore, by ^{123}I-IBZM SPECT showing a reduced rate of progressive loss of dopamine-D2 receptor binding sites in the neostriatum.

From the scientific point of view, these results give unique insight into the pathophysiology of extrapyramidal movement disorders as well as the changes associated with progression of the different diseases. The decline of IBZM binding observed in parkinsonian plus syndrome patients compared to the unaffected binding in Parkinson's disease patients allows the estimation and quantification of the progression rates of the postsynaptic pathology associated with these diseases. Due to the small number of patients we studied, as well as the technical limitations of the systems used in our study, our results must be taken with caution and several points have to be discussed.

Clinical Consideration

Since clinical diagnosis is uncertain in some patients with extrapyramidal movement disorders, we selected only those patients in whom the diagnosis of Parkinson's disease or parkinsonian plus syndrome was clinically reliable. The patients included in our study met the criteria of the United Kingdom brain bank and the criteria of Quinn and Steele for Parkinson's disease, multiple system atrophy and progressive supranuclear palsy, respectively (*1,10,12*).

In a recent article, Schwarz et al. (*22*) reported the effects of midterm dopaminergic therapy on striatal binding of IBZM. In patients with Parkinson's disease treated with a combination of L-Dopa and a dopamine agonist, they found a reduction of approximately 7% over a period of 3–6 mo suggesting a down-regulation of the binding capacity of striatal dopamine-D2 receptors. This contrasts with what we found with a longer follow-up period (mean = 36 mo) for Parkinson's disease patients. Their results were obtained from a limited number of patients (n = 19) and may not be applicable to long-term follow-up studies or to different pathologic entities (i.e., parkinsonian plus syndrome).

All but three patients with Parkinson's disease and two with parkinsonian plus syndrome in our study had been treated for at least 2 yr before the first SPECT study in contrast to the initially untreated population studied by Schwarz et al. (*22*). It seems unlikely that after at least 2 yr of treatment and an additional follow-up of 11–53 mo there would still be such a continuous loss of binding capacity. However, since the the patients included in our study were mostly in an advanced stage of the disease at the time of their first SPECT examinations, we cannot entirely eliminate that the down-regulation might have occurred earlier in their disease process. Additional follow-up studies looking first at patients before initiation of dopaminergic therapy might give better insight into the widely discussed matter of down-regulation.

The changes observed by Schwarz et al. (*22*) underline this interpretation of early down-regulation since they may represent an initial pharmacologic effect in previously untreated patients. Similar findings have been published previously by our group (*19*).

Two patients with parkinsonian plus syndrome presented with increased binding at their follow-up SPECT study. One of these patients had no specific binding on the initial scan (NS/CB = 1.04), and even the follow-up scan showed almost no specific uptake within the neostriatum (NS/CB = 1.13). We consider both results as absent specific binding. The interpretation of the second patient with increased receptor binding on follow-up was more difficult. Up-regulation of receptor sensitivity due to a lack of intrasynaptic dopamine has been proposed in Parkinson's disease patients (*19*), but this phenomenon was not reproduced in our other parkinsonian plus syndrome patients.

The age-dependent variation of D2-receptors has been studied with controversial results in the literature (*15,23*). Consistent with our previous studies, no correlation was found between the age and striatal receptor binding in either group (*14*), and both were advanced in age. An age-dependent decline has only been reported during the first three to four decades of life, while in elderly individuals no further decrease has been described (*15,23*). However, our study sample is not large enough to either address the possible effects of aging or to correct the SPECT results for aging.

Methodological Consideration

Potential limitations of longitudinal studies include the introduction of a systematic error over the period of observation (*20*). To avoid this bias, we made a special effort to assess the variability and reproducibility of the scan and evaluation process. Particular attention was given to correcting for different positioning of the follow-up scans compared to those in the initial study (*14*).

The limited image quality that does not allow the differentiation of anatomical structures and the high scatter counts due to relatively low counting rates could limit the overall clinical use

of this setting. However, several studies (*14*) have proven the usefulness and the clincal relevance of results obtained from these SPECT systems despite the above cited limitations. Not all nuclear medicine facilities have more advanced camera systems. Therefore, it is important to underline the capacity and improve the quality of single-headed gamma camera systems by refining the reconstruction and evaluation algorithms.

We used a semiautomated reconstruction algorithm that we proved had a sufficiently low intra- and interobserver results variance. We also found this algorithm to be relatively independent from either the experience of the user or the tracer uptake itself.

Since only two data points were available for each patient, a linear evolution of D2-receptor changes was assumed. This may have oversimplified the pathophysiologic mechanisms associated with ongoing diseases. However, this approach has been considered reasonable for the brief follow-up period by other investigators (*20*).

The time interval between scans varied from 11–53 mo. The reason for this limitation was the routine follow-up schedule for outpatients in our clinic. The logistical problems as well as the economic aspects of additional appointments for the patients represented an unfavorable bias.

CONCLUSION

We found that in vivo assessment of striatal dopamine-D2 receptors at an advanced stage of different extrapyramidal movement disorders allowed better discrimination of these different entities than earlier stages of these diseases. Patients with Parkinson's disease maintained a constant dopamine-D2 receptor binding as measured by ^{123}I-IBZM SPECT. In parkinsonian plus syndrome, the striatal loss of dopamine-D2 receptors, as assessed by ^{123}I-IBZM SPECT, progresses during the course of the disease. Long-term medication of L-Dopa alone or in combination with a D2 agonist seemed not to alter the binding of striatal dopamine-D2 receptors in patients with Parkinson's disease.

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