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[123I]β-CIT and SPECT in essential tremor and Parkinson's disease

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Summary. Resting and postural tremor may occur in essential tremor (ET) and Parkinson's disease (PD). The aim of the present study was to investigate the cocaine derivative [123I]β-CIT, which labels striatal dopamine transporters, and SPECT in differentiating these diseases.

Methods: 30 healthy volunteers, 32 patients with ET and 29 patients with idiopathic PD of Hoehn/Yahr stage I were investigated. Specific over nondisplaceable binding ratios (target/cerebellum-1) were calculated for the striatum, the caudate nucleus and the putamen separately as well as a ratio putamen/caudate and the percent deviation of each patient's ratio from age-expected control values.

Results: Striatal [123I]β-CIT binding ratios in ET were within normal ranges and showed only a discrete elevation to age-expected control values (+14.6%). In PD significantly reduced specific binding was evident not only contralaterally to the clinically affected side (putamen: −62%, caudate nucleus: −35%), but also ipsilaterally (putamen: −45%, caudate nucleus: −22%). All investigated parameters differed significantly between PD and controls and ET respectively.

Conclusion: Imaging striatal dopamine transporters with [123I]β-CIT and SPECT could clearly distinguish between ET and PD in an early stage of the disease. Findings do not suggest a subclinical involvement of dopaminergic nigrostriatal neurons in ET.

Keywords: [123I]β-CIT, SPECT, essential tremor, Parkinson's disease.

Introduction

Tremor is a symptom frequently encountered in clinical neurology. It is one of the features of Parkinson's disease (PD) and atypical parkinsonian syndromes, especially of multiple system atrophy. Even dystonia may be associated with tremor (Jankovic et al., 1991). Essential tremor (ET) is referred to

as the most common movement disorder (Hubble et al., 1989). Additionally other types of tremor such as drug-induced tremor, physiological tremor, orthostatic tremor or tremor related to other neurological or internal diseases have to be distinguished. Although these diseases usually can be distinguished easily because of distinct course and clinical symptomatology a differential diagnosis can sometimes be difficult.

In ET, postural or kinetic tremor of the hands, head or other parts of the body can be found, occurring sporadically or with autosomal dominant transmission (Hubble et al., 1989). A relationship of this disease to other movement disorders such as PD or dystonia has been repeatedly discussed (Geraghty et al., 1985; Cleeves et al., 1988; Koller et al., 1989; Jankovic et al., 1991; Dürr et al., 1993; Pahwa et al., 1993; Rajput et al., 1993; Koller et al., 1994). But neuropathological data do not confirm an association between ET and PD, as no histological abnormalities ín the substantia nigra such as neuronal loss and Lewy body inclusions have been found in ET (Rajput et al., 1993).

PD is characterized by a loss of pigmented cells in the lateral part of the substantia nigra pars compacta (Duvoisin and Golbe, 1989; German et al., 1989; Goto et al., 1989) resulting in a loss of dopaminergic neurons projecting to the striatum. Consequently, the dopaminergic nerve endings and presynaptically located dopamine transporters in the striatum are diminished (Pimoule et al., 1983; Janowski et al., 1987; Maloteaux et al., 1988; Kaufmann and Madras, 1991; Niznik et al., 1991). Patients with PD can demonstrate resting and postural tremor similar as in ET (Koller et al., 1989). As in ET a resting tremor component and cogwheel rigidity on synkinesia may occur as well (Salisachs et al., 1984), a differentiation of these diseases may be difficult in some cases on clinical grounds, especially in early stages of the diseases.

Recently a group of cocaine analogs with very high affinity for monoamine transporters have been developed as tracers for positron and single-photon emission tomography (PET, SPECT respectively). Of these 2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane (β-CIT, RTI-55) (Neumeyer et al., 1991; Shaya et al., 1992) received a lot of interest for the in vivo investigation of PD. β-CIT has been shown to bind with high affinity to dopamine (DA) and serotonin (5-HT) transporters (Neumeyer et al., 1991; Boja et al., 1991; Shaya et al., 1992; Scheffel et al., 1992; Laruelle et al., 1993). Binding is highest in the striatum, where β-CIT almost exclusively labels DA transporters, and in the brainstem, where it binds to 5-HT transporters (Laruelle et al., 1993). Using β-CIT it was possible to visualize and quantify the degeneration of the dopaminergic striatal system in PD and to correlate it with measures of clinical severity either taking striatal β-CIT binding (Brücke et al., 1993; Kuikka et al., 1993; Asenbaum et al., 1997) or β-CIT binding in putamen and caudate nucleus separately (Seibyl et al., 1995).

The aim of the present study was to investigate the use of [^{123}I]β-CIT and SPECT in ET and early PD a) to describe possible alterations of the dopaminergic system in ET, b) to discuss [^{123}I]β-CIT binding in early stages of PD, and c) to evaluate the application of this method for an early differentiation between ET and PD.

Methods

Subjects

30 healthy volunteers (20 female, 10 male, age range 21–75 years, mean age 45 years), 29 patients with idiopathic PD (10 female, 19 male, age range 39–81 years, mean age 61 years) and 32 patients with ET (19 female, 13 male, age range 31–83 years, mean age 63 years) were investigated with [123I]β-CIT and SPECT. The volunteers were free of medication and had no neuropsychiatric disorders in their history with the exception of peripheral neurological disorders. – The patients were examined neurologically by two experienced physicians (T.B., W.P.). Severity of disease was classified according to Hoehn and Yahr (H/Y) (Hoehn and Yahr, 1967). All patients were in H/Y stage I with a mean duration of 1.8 years (ranging between 0.3 and 5 years). Patients were free of major depressive illness, dementia or other neurological signs besides parkinsonism. Motor disabilities and activities of daily living were rated off medication with the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987). Patients demonstrated a mean motor score of 9.9 (+ −3.8) and a mean activities of daily living score of 5.7 (+ −2.8).

12 patients with PD were untreated or stopped therapy 24 hours before tracer administration, the remaining patients were under antiparkinsonian medication with L-DOPA/decarboxylase inhibitors of various doses (n = 15), sometimes in combination with dopamine agonists (n = 3) or amantadine (n = 2) and anticholinergic drugs (n = 5) except benztropine. Three patients were treated with a tetracyclic antidepressant. Laruelle et al. (1993) could not delineate an influence of L-DOPA on β-CIT binding and there is until now no evidence that the other drugs interfere with β-CIT at the DA transporter. Therapy with l-(−)-deprenyl in 8 patients was discontinued at least 18 hours before [123I]β-CIT application to avoid interaction of its metabolites with β-CIT at the DA transporter (Laruelle et al., 1993) (see Table 1).

All patients with tremor suffered from postural tremor, more than the half additionally demonstrated resting tremor as well. According to the diagnostic criteria of the Tremor Investigation Group (Findley, 1996) patients with ET were classified into three groups: patients with definite ET (n = 13) (ET I), with probable ET (n = 8) (ET II) and possible ET (n = 11) (ET III). In contrast to these criteria patients with possible ET in this study were not allowed to demonstrate other neurological signs than tremor, so that only duration of tremor distinguished ET II from ET III. Clinical data are summarized in Table 2. None of the ET patients received tremorogenic drugs. 5 patients were completely untreated, 6 patients took β-blockers, 5 others L-DOPA/decarboxylase inhibitors. Two patients were under antidepressant medication with tetracyclic antidepressants. The remaining patients received various drugs for treatment of other medical conditions. Cerebral computed tomography (CT) was normal in all instances.

The study was approved by the local ethical committee and informed consent was obtained from each person.

SPECT investigation

After blockade of thyroid uptake subjects received a mean dose of 133 MBq (+ −28.6) of [123I]β-CIT intravenously as a bolus.

All persons were investigated 20 (+ −1) hours (Asenbaum et al., 1997) after tracer administration. SPECT studies were performed with a triple-headed rotating scintillation camera (Siemens Multispect 3, FWHM 9 mm) equipped with medium-energy collimators and a dedicated computer system. Imaging lasted for 40 minutes (40 sec per frame), so that 180 frames were achieved in a step and shoot mode. The subject's head was positioned in a head holder using a crossed laser beam system for repositioning. Parallel to the cantho-meatal plane 3.5 mm thick cross sections were reconstructed by filtered back projection in 128 × 128 matrices using a Butterworth filter (cutoff frequency 0.7, order 7).

Table 1. Clinical data of patients with Parkinson's disease, Hoehn/Yahr stage I

nb	age, gender	side	dur	UPDRS: M/A	therapy at [^{123}I]β-CIT application
1	70, f	ri	0.3	11/7	0
2	47, m	ri	1	6/6	0
3	68, f	ri	5	12/2	D, DA, A
4	52, m	ri	3	9/10	D, AC, AD
5	56, f	ri	3	8/4	D
6	51, f	ri	4	16/12	D, DA, A, AD
7	70, m	le	4	10/10	D, AC
8	68, m	ri	1	9/2	D
9	61, f	le	0.5	6/3	0
10	53, m	le	2	7/3	D
11	74, m	le	1	8/2	0
12	52, m	le	0.5	7/4	0
13	42, m	ri	3	12/10	D
14	39, m	le	0.5	16/5	AC
15	55, m	ri	0.5	12/8	D
16	45, m	ri	0.5	3/3	0
17	81, m	ri	2	11/6	D, AC
18	77, f	ri	2	14/5	D
19	66, m	ri	0.5	11/6	0
20	54, m	le	2	9/7	D
21	67, f	le	4	8/3	D
22	71, m	ri	1.5	11/6	0
23	64, m	le	0.5	8/5	0
24	61, f	ri	1	2/2	0
25	74, m	ri	3	5/6	D, AD
26	65, m	ri	2.5	12/10	D
27	66, f	ri	1	13/8	0
28	55, f	le	1	11/5	DA, AC
29	54, m	le	1	19/6	0

nb patient number, *side* side of parkinsonian symptoms, *dur* duration of the disease in years, *therapy* therapy during investigation, *UPDRS* Unified Parkinson's Disease Rating Scale, *M* motor score, *A* activity of daily living score, *m* male, *f* female, *ri* right, *le* left, *0* no therapy, *D* L-DOPA/decarboxylase inhibitor, *DA* dopamine agonist, *A* amantadin, *AC* anticholinergic drug, *AD* antidepressant therapy

Attenuation correction was then performed with a uniform attenuation coefficient of 0.12/cm after manual drawing an ellipse around the head contour.

Regions of interest (ROIs) were drawn manually on single slice views by one investigator (S.A.), blinded to the diagnosis, over the right and left striatum (size: 40–45 pixels each) and the cerebellum respectively (size: 50–55 pixels each) using a brain atlas for help. Striatal ROIs were drawn on several consecutive (3.5 mm thick) axial slices and the highest counts/pixel for each striatum were taken to avoid tilting errors. Additionally a subregional analysis of the [^{123}I]β-CIT uptake in the caudate nucleus and the putamen was performed on both sides applying standardized ROIs (size: 3×3 pixels each). Cerebellar ROIs were drawn on the slice of best visualization, usually 10 slices below the striatum, and on the two adjacent slices. These three consecutive sections and right and left cerebellar hemispheres were pooled together, and average cerebellar counts were calculated. Cerebellar values were taken as reference (nondisplaceable activity), because

Table 2. Clinical data of patients with essential tremor, classified into definite, probable or possible essential tremor

nb	age, gen	post	kinetic	rest	local	dur	fam.hist	add
definite								
1	74, m	++	++	+	U, M	10	−	
2	76, f	+	+	+	U, ri > le	10	+	
3	72, f	+		+	U	5	−	
4	83, m	++	++	+	U, le > ri	70	+	
5	56, m	+			U	45	+	
6	51, f	+	+		U	10	+	
7	63, m	+	+		U, L	40	+	
8	81, m	++	+	+	U	10	−	
9	34, m	+		+	U, le > ri	10	−	
10	67, f	+		+	U, H	20	−	
11	54, m	++	++	+	U, le > ri	10	n.k.	
12	66, f	+	+		U, H, le > ri	20	+	
13	54, m	++	+		U > L	30	+	
probable								
1	31, m	+	+		U, H	4	+	
2	61, f	+	+	+	U, ri > le	3	n.k.	
3	68, m	+		+	U, ri > le	3	−	
4	43, f	+		+	U	4	n.k.	
5	52, f	+	+	+	U, le > ri	3	+	
6	78, f	++	++	+	U, L	3	+	
7	78, f	+			U, L	3	−	
8	66, m	+	+		U, L, H, le > ri	3	n.k.	
possible								
1	47, f	+		+	U, ri > le	2	+	
2	74, f	+	+	++	U	1	n.k.	
3	33, m	++	+		U, ri > le	0.25	−	
4	58, f	+	+		U, ri > le	2	−	PD+
5	72, f	++	+	++	U, H	1	n.k.	
6	67, f	+			U, le < ri	0.25	−	
7	81, f	+			U, le > ri	0.4	n.k.	
8	64, f	+			U, H	1	n.k.	
9	67, f	+		+	U, ri	0.5	n.k.	
10	73, m	+		+	U, ri > le	2	−	PD+
11	76, f	+	+		U, ri > le	2	+	

nb patient number, *gen* gender, *post, kinetic, rest* postural, kinetic, resting tremor, *local* tremor localisation, *dur* duration of the disease, *fam.hist* familial history of essential tremor, *add* additional remarks, *m* male, *f* female, +, ++ = positive, − = absent, *U, L* upper, lower extremities, *M* mouth, *H* head, *ri* right, *le* left, *n.k.* not known, *PD+* positive familial history of Parkinson's disease

postmortem studies (Palacios et al., 1988; deKeyser et al., 1989) had shown a very low density of DA (and 5-HT) transporters in this region.

For semiquantification three different methods of describing brain activity were applied: 1) the binding ratios striatum over cerebellum minus 1 (SC ratio) as well as putamen and caudate nucleus over cerebellum minus 1 (PC and CC ratio) were calculated initially for both sides, which represent specific/nondisplaceable binding (according to

Leenders et al., 1990) and which are directly related to binding potential during a period of binding equilibrium (Laruelle et al., 1994). Reproducibility of striatal [^{123}I]β-CIT measurements have been confirmed by Seibyl et al. (1996), although calculating striatal over occipital cortex binding ratios. The approach of calculating three binding ratios was choosen to compare their sensitivity concerning disease detection. 2) Age-expected control values were obtained from regression analysis of the binding ratios (SC, PC, CC) of the healthy volunteers. The percent deviation of each patient's binding ratios from this age-expected control value was calculated. 3) Furthermore a ratio PC over CC (p/c ratio) was obtained.

Statistical analysis

In controls and patients with ET the binding ratios SC, PC and CC and the p/c-ratio of the left and right side, in PD patients the ratios ipsi- and contralateral to clinical symptoms were compared intraindividually using the Student's t-test for paired data. For further calculations in controls and ET patients the values of the left and right side were pooled together, in patients with PD values of the ipsi- and contralateral side as well as mean values were considered. The age-related decline of binding ratios (SC, PC and CC) and p/c ratio was evaluated in controls and ET patients by regression analysis. Binding ratios (SC, PC, CC), p/c ratio and percent deviation to age-expected control values of binding ratios were compared between the controls and the patient groups and between the ET groups seperately applying a one-way ANOVA. Additionally in patients with ET III SC, CC and p/c ratios were compared with corresponding values ipsilaterally to clinical symptoms in PD performing a one-way ANOVA. Finally separate linear discriminant function analyses were calculated for SC, PC and CC (in PD ipsi- and contralateral to clinical symtoms) as well as p/c ratio comparing controls and patient groups.

$P < 0.05$ was regarded as statistically significant.

Results

Visual evaluation

In all pts with PD relatively high activities were found in the caudate nucleus, whereas the putamen could hardly be differentiated. The striatum contralateral to clinical symptoms was more severly affected in all cases than the ipsilateral striatum. No abnormalities in the visualization of the basal ganglia could be seen in ET (see Fig. 1).

Control group

Neither the SC, PC, CC nor the p/c ratio showed a significant left/right asymmetry, so that the values were pooled together. Controls demonstrated a striatal binding ratio (SC) of $r = 8.57$ ($+ -1.76$) with a significant age-dependent decline of 6% per decade ($R^2 = 0.541$, $p < 0.001$), which was similar for the CC and PC ratio (decline/decade CC: 6.0%, PC: 6.4%). The p/c ratio did not change during aging ($R^2 = 0.072$, $p < 0.15$). Mean values are listed in Table 3.

ET group

Age did not differ significantly between the three ET groups ($F = 0.31$, $p < 0.73$). Binding ratios (SC, PC, CC) and p/c ratio showed no left/right asymmetry as well as no differences between the three ET groups (for instance SC

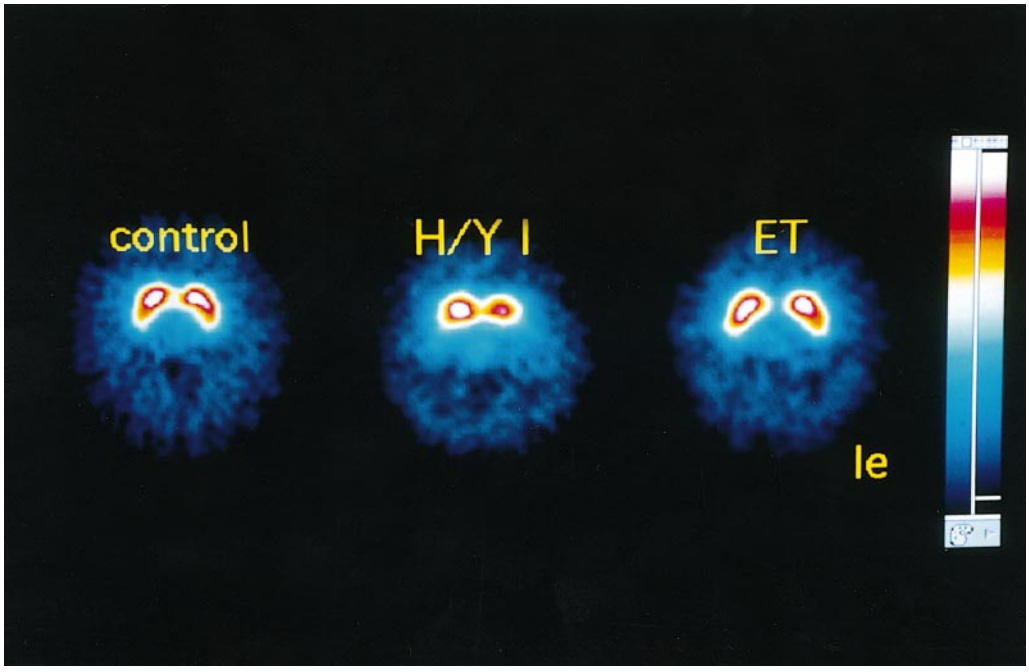

Fig. 1. [123I]β-CIT SPECT in a healthy volunteer (control), a patient with Parkinson's disease of H/Y stage I and a patient with essential tremor (ET) (*le* left)

Table 3. [123I]β-CIT binding ratios (striatum, putamen and caudate nucleus over cerebellum-1), ratio putamen/caudate nucleus, and percent deviation of SC binding ratio to age-expected control values in healthy volunteers and in patients with Parkinson's disease and essential tremor (left/right mean values + −s.d.)

	binding ratio SC	binding ratio PC	binding ratio CC	p/c ratio	% deviation SC
control	8.57 + −1.76	7.93 + −1.69	10.09 + −2.10	0.787 + −0.05	
ET definite	7.99 + −1.26	7.56 + −1.45	9.66 + −1.41	0.781 + −0.07	+10%
ET probable	8.94 + −1.62	8.43 + −1.46	10.92 + −2.24	0.778 + −0.06	+18%
ET possible	8.49 + −1.90	7.85 + −1–64	10.61 + −2.39	0.744 + −0.04	+18%
ET all	8.40 + −1.59	7.88 + −1.51	10.30 + −2.01	0.768 + −0.06	+15%
PD	4.50 + −0.78	3.15 + −0.73	6.29 + −1.11	0.569 + −0.07	−40%

ET essential tremor, *PD* Parkinson's disease, *SC* ratio (striatum/cerebellum-1), *PC* ratio (putamen/cerebellum-1), *CC* ratio (caudate nucleus/cerebellum-1), *p/c* ratio PC/CC

binding ratio: ET I: r = 7.99, ET II: r = 8.94, ET III: r = 8.49; F = 0.92, p < 0.41; see also Table 3). Additionally percent deviation of SC ratio to age-expected control values revealed no significant differences between the three ET groups (ET I: +10%, ET II: +18%, ET III: +18%; F = 0.76, p < 0.48). Consequently for further calculations data of these three patients groups with ET were pooled together as well. – An age-dependent decline of all binding

ratios was evident (5.5% per decade, for instance age dependency of SC ratio: $R^2 = 0.36$, $p < 0.0003$), whereas the p/c ratio remained stable ($R^2 < 0.01$, $p < 0.96$).

PD group

The binding ratios (SC, PC, CC) as well as the p/c ratios were significantly lower contralaterally to clinical symptoms than ipsilaterally (SC binding ratio: $r = 4.01$ vs. $r = 4.94$, $t = -10.46$, $p < 0.0001$; PC binding ratio: $r = 2.57$ vs. $r = 3.74$, $t = -8.87$, $p < 0.0001$; CC binding ratio: $r = 5.72$ vs. $r = 6.86$, $t = 10.51$, $p < 0.0001$; p/c ratio: $r = 0.45$ vs. $r = 0.54$, $t = 4.24$, $p < 0.0002$; contralateral vs. ipsilateral) (for mean values see Table 3).

Comparisons between PD, ET and control group

Age differed significantly between the controls and the patients ($F = 13.37$, $p < 0.001$). ANOVA of the binding ratios (SC, PC, CC) and the p/c ratio of these groups revealed significant differences between the PD group and the controls and ET patients respectively (SC binding ratio: $F = 75.02$, $p < 0.0001$; PC binding ratio: $F = 116.18$, $p < 0.0001$; CC binding ratio: $F = 46.4$, $p < 0.0001$; p/c ratio: $F = 149.03$, $p < 0.0001$) (Fig. 2).

Comparing the data of the three ET groups and the control group using an ANOVA the SC, CC and PC binding ratio and the p/c ratio demonstrated no differences. The SC binding ratio in ET was slightly elevated as compared to age-expected control values (+14.6%).

Values for the ipsi- and contralateral striatum were significantly reduced in PD patients in comparison to normals on both sides (SC binding ratio ipsi:

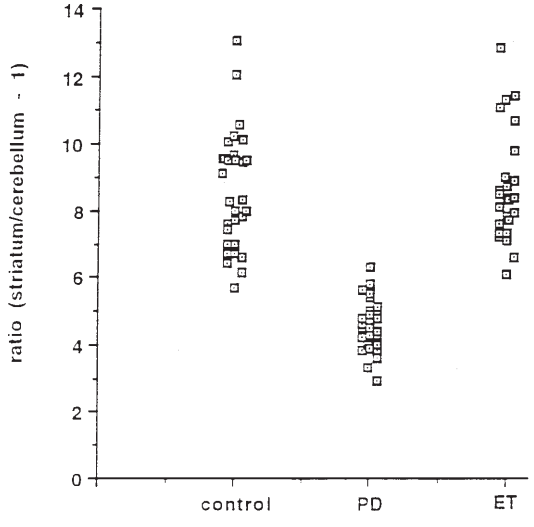

Fig. 2. Individual striatal [^{123}I]β-CIT binding ratios (striatum/cerebellum-1, SC; left/right mean values) of control group and patients with Parkinson's disease of H/Y stage I (PD) and essential tremor (ET) respectively

$F = 99.0$, $p < 0.0001$; contra: $F = 171.14$, $p < 0.0001$; PC binding ratio ipsi: $F = 138.77$, $p < 0.0001$; contra: $F = 263.38$, $p < 0.0001$; CC binding ratio ipsi: $F = 51.76$, $p < 0.0001$; contra: $F = 101.86$, $p < 0.0001$; p/c ratio ipsi: $F = 101.2$, $p < 0.0001$; contra: $F = 263.4$, $p < 0.0001$). In comparison to age-expected control values patients with PD demonstrated a significant percentual decrease of striatal [123I]β-CIT binding ipsilaterally of 34% and contralaterally of 46%, which was most pronounced in the contralateral putamen (PC ratio: −62%, CC ratio: −35%) and less marked in the ipsilateral caudate nucleus (CC ratio: −22%, PC ratio: −45%).

Applying ANOVA the comparison of the three ET groups and the patients with PD revealed significant differences in all calculated parameters (for instance SC contralateral to clinical symptoms: $F = 65.3$, $p < 0.0001$, SC ipsi: $F = 36.7$, $p < 0.001$). Taking all patients with ET together the investigated binding ratios (SC, PC, CC, p/c on both sides) were significantly higher than in patients with PD (for instance CC ipsi: $F = 63.2$, $p < 0.0001$; PC ipsi: $F = 155.0$, $p < 0.0001$). A direct comparison of individual data as demonstrated in Figs. 2 and 3 for SC ratios and percent deviation to age-expected control values revealed nearly no overlap of these data in PD and ET. Taking means of SC ratio + −2 standard deviations a sensitivity of separating PD and ET of 80% and a specificity of 100% could be achieved, taking p/c ratio the sensitivity could be raised to 93%. – A particular comparison of the SC and CC binding ratios and the p/c ratio ipsilaterally to clinical symptoms in PD and the corresponding values of patients with ET III revealed significant differences as well (SC binding ratio: $F = 64.9$, $p < 0.0001$; CC binding ratio: $F = 42.5$, $p < 0.0001$; p/c ratio: $F = 42.1$, $p < 0.0001$).

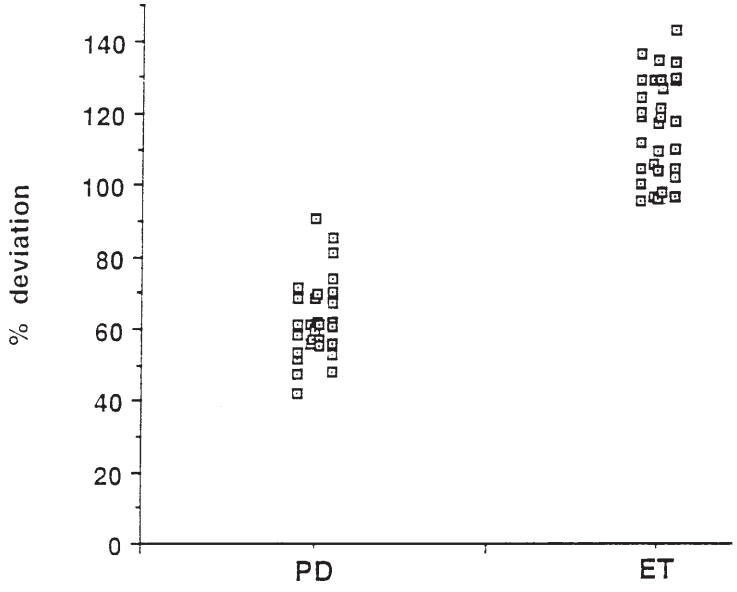

Fig. 3. Percent deviation of each patient's striatal [123I]β-CIT binding ratio (striatum/cerebellum-1, SC; left/right mean values) to age-expected control values in Parkinson's disease of H/Y stage I (PD) and essential tremor (ET)

Table 4. Discriminant function analyses in controls and patients with Parkinson's disease of H/Y stage I and essential tremor

	canonical correlation	univariate F ratio	Wilks' lambda		percent of cases correctly classified
Con vs. PD			separate	overall	overall
PC contra	0.91	263.4[a]	0.178	0.093	100%
CC contra	0.80	101.9[a]	0.359		
PC ipsi	0.84	132.8[a]	0.300		
CC ipsi	0.69	51.8[a]	0.524		
SC mean	0.84	131.6[a]	0.303	0.150	98.3%
p/c mean	0.89	214.1[a]	0.210		
Con vs. ET					
PC mean	0.02	0.02	0.999	0.963	
CC mean	0.05	0.15	0.997		
SC mean	0.05	0.17	0.997	0.997	59.7%
p/c mean	0.01	0.007	0.999		
ET vs. PD					
PC contra	0.92	317.6[a]	0.157	0.092	100%
CC contra	0.82	120.6[a]	0.328		
PC ipsi	0.85	155.0[a]	0.276		
CC ipsi	0.72	63.1[a]	0.483		
SC mean	0.84	143.6[a]	0.291	0.134	98.4%
p/c mean	0.88	211.4[a]	0.218		

[a] $p < .0001$. *Con* healthy volunteers, *PD* Parkinson's disease, *ET* essential tremor, *SC* ratio (striatum/cerebellum-1), *PC* ratio (putamen/cerebellum-1), *CC* ratio (caudate nucleus/cerebellum-1), *p/c* ratio PC/CC, *contra/ipsi* contra/ipsilateral to clinical symptoms, *mean* left/right mean values

Results of separate discriminant function analyses are listed in Table 4, demonstrating the highest discriminative power of contralateral PC binding ratio and of p/c ratio for distinguishing PD from controls and ET respectively (PC: $r = 0.91$ and $r = 0.92$, p/c: $r = 0.89$ and $r = 0.88$; PD versus controls and ET, $p < 0.0001$), whereas ipsilateral CC binding ratio showed the least discrimination ($r = 0.69$ and $r = 0.72$; PD versus controls and ET, $p < 0.0001$). Taking PC and CC binding ratios contra- and ipsilaterally to clinical symptoms as factors together all PD patients were correctly classified. SC binding ratio and p/c ratio as factors discriminated PD patients with high significance, correctly predicting the group membership in 98.3% (PD versus controls and ET); even taking SC binding ratio alone 94.9% (PD versus controls) and 96.7% (PD versus ET) respectively were correctly classified. No significant discrimination of controls and ET patients could be achieved.

Discussion

The pathophysiology of ET is not fully understood and no neuropathological abnormalities in the substantia nigra, cerebellum, inferior olives and red

nucleus have been found so far in autoptic studies (Larsen and Calne, 1983; Rajput et al., 1993). The existence of a central tremor generator has been discussed, but it seems likely that not a single generator but an altered network function causes ET. So using PET and [15O]CO_2 (Colebatch et al., 1990; Jenkins et al., 1993), [15O]H_2O (Boecker et al., 1996) or applying [18F] fluoro-2-deoxyglucose (Dubinsky and Hallett, 1987) it was possible to demonstrate an activation of the cerebellum and the inferior olivary nucleus in essential tremor interpreted as a sign of an olivocerebellar oscillation. On the other side Wills et al. (1994, 1995) were not able to delineate an activation of the inferior olivary nucleus, but of the midbrain in the region of the red nuclei, of the cerebellum and of the thalamus during tremor.

In the present study we investigated the dopaminergic nigrostriatal system of patients with ET using [123I]β-CIT. In a first step patients divided clinically into definite, probable and possible ET were compared. No difference in striatal [123I]β-CIT binding between these tremor groups were found. Thus patients with isolated postural tremor of short duration could not be distinguished from those with definite ET. In comparison with controls, patients with ET did not demonstrate different striatal [123I]β-CIT binding ratios, although the data showed an elevation of 15% to age-expected control values. Discriminant functional analyses were not able to separate controls and patients with ET, neither taking PC, CC nor SC binding ratios. Investigating different parts of the nigrostriatal system using PET and 6-L-[18F]fluoro-DOPA ([18F]-FDOPA) Brooks (1991) could not find altered striatal [18F]-FDOPA uptake in 8 patients with familial tremor, indicating a normal function of the aromatic amino acid decarboxylase and normal uptake and metabolism of exogenous DOPA in dopaminergic nigrostriatal terminals of patients with ET. In patients with sporadic postural tremor a great majority had normal [18F]-FDOPA uptake in the putamen (Brooks et al., 1992). By investigating the density of the dopaminergic nerve endings in the striatum our results in patients, as well with definite ET as with pure postural tremor, confirm these studies, which argues against the possibility of an involvement of this system in ET.

An association between ET and PD has been discussed repeatedly, suggested (Geraghty et al., 1985; Koller et al., 1994; Lou and Jankovic, 1991; Jankovic et al., 1995) or rejected (Cleeves et al., 1988; Pahwa and Koller, 1993; Rajput et al., 1993; Bain et al., 1994) in several clinical studies. Geraghty et al. (1985) claimed a 24 times greater risk of ET patients for developing PD. Koller et al. (1994) described a higher frequency of PD in ET than reported for the general population (approximately 6% vs. 0.2–1%). On the contrary Cleeves et al. (1988) negated any association between ET and PD demonstrating no increased frequency of PD in patients with ET and no familial burden for either disease. Bain et al. (1994) failed to demonstrate a connection between ET and PD and DT respectively.

In the present study the investigation of patients with PD in H/Y stage I using [123I]β-CIT demonstrated reduced [123I]β-CIT binding in the striatum indicating diminished dopamine transporters in the whole striatum, mainly in the putamen and pronounced on the side contralaterally to clinical symptoms.

These results are in accordance with former studies evaluating dopamine reuptake sites in PD using [^{123}I]β-CIT (Brücke et al., 1993; Innis et al., 1993; Kuikka et al., 1993; Seibyl et al., 1995; Asenbaum et al., 1997; Rinne et al., 1995). Regarding dopamine transporters as a measure of regional density of dopaminergic nerve endings these findings are confirmed by postmortem findings which delineated a more pronounced loss of neurons in the ventrolateral part of the substantia nigra, primarily projecting to the posterior putamen (Bernheimer et al., 1973; Hornykiewicz and Kish, 1986; Kish et al., 1988; German et al., 1989; Goto et al., 1989; Rinne et al., 1989). Asymmetric affection of the striatum in early stages of PD, which is pronounced in the putamen, has been reported earlier (Garnett et al., 1984; Karbe et al., 1992) and seems to be related to asymmetric cell loss in the substantia nigra, which has been found postmortem in correlation to asymmetrical disease onset (Kempster et al., 1989).

The results of discriminant functional analyses, correctly classifying even PD patients of H/Y stage I against controls in a very high percentage, are in accordance with a study of Seibyl et al. (1995) investigating patients with higher disease severity as well. The strongest discriminative power of the PC binding ratio contralateral to clinical symptoms was confirmed, but even the mean SC binding ratio alone correctly separated 95% of PD patients and controls.

In comparison with age-expected control values the specific [^{123}I]β-CIT binding in the striatum showed a mean reduction of 40% with a decrease of 34% ipsilaterally to clinical symptoms and of 46% contralaterally. Considering the specific binding of the caudate nucleus and the putamen separately the largest reduction was found in the contralateral putamen (−62% to age-expected control values) and the smallest in the ipsilateral caudate nucleus (−22%). Brooks et al. (1992) described a reduction of 49% of the average [^{18}F]-FDOPA uptake in the putamen of patients with isolated rest tremor and of 23% in the caudate nucleus, which is comparable to results of the present study (mean −53.5% in the putamen, mean −28.5% in the caudate nucleus). Applying [^{123}I]β-CIT Marek et al. (1996) described a similar reduction of specific [^{123}I]β-CIT binding in the putamen and caudate nucleus in patients with hemiparkinsonism as found in this study, which ranged between 58% for the putamen contralaterally to clinical symptoms and 22% for the ipsilateral caudate nucleus. Therefore all these results seem to indicate a threshold of about 50–60% loss of nigroputaminal dopaminergic neurons to develop clincial signs of PD. Postmortem findings support this presumption describing a 60%–70% loss of neurons in the lateral part of the substantia nigra pars compacta (German et al., 1989; Goto et al., 1989; Karbe et al., 1992), although obtained in patients with more severe PD.

It was possible to visualize a subclinical lesion of the nigrostriatal system as the specific binding of [^{123}I]β-CIT was reduced in the putamen contralaterally to the clinically not affected body side as well; even the caudate nucleus was affected. Thus the question arises whether it will be possible to identify presymptomatic patients, who will develop PD.

A clear difference in the striatal [123I]β-CIT uptake between patients with PD and ET was evident, even when patients with possible ET were taken separately for comparison. No patient with ET demonstrated the pathological uptake pattern with reduced [123I]β-CIT binding in the putamen as visible in PD, which makes a differentiation of these two diseases easy. Discriminant functional analyses separeted PD and ET patients with the same high accuracy as PD patients and controls. Using the ratio putamen over caudate nucleus a sensitivity of 93% and a specifity of 100% could be achieved. The specific binding of [123I]β-CIT in the striatum and the caudate nucleus or the putamen respectively was significantly lower in PD than in ET. Even the caudate nucleus ipsilaterally to clinical symptoms in PD demonstrated a significantly reduced [123I]β-CIT binding in comparison to patients with possible ET and in these cases with postural tremor. Similar findings have been reported by Brooks et al. (1992), who delineated reduced putaminal [18F]-FDOPA uptake in patients with isolated rest tremor as seen in PD, whereas in patients with sporadic postural tremor a great majority had normal [18F]-FDOPA uptake in the putamen. So the possibility of investigating the dopaminergic system by using [123I]β-CIT and the SPECT technique now seems to allow an early differentiation between PD and ET. To make conclusions possible, in this study patients with possible ET were not allowed to demonstrate other additional neurological signs than tremor. However especially in patients who exhibit other additional neurological signs besides tremor [and who could be classified as possible ET according to Findley (1996) too], this method can now be applied for differential diagnosis, and therefore offers a valuable tool in uncertain cases or in cases with short duration of the disease. As described above it was possible to demonstrate subclinical degeneration of dopaminergic nigrostriatal neurons in hemiparkinsonism. In our population of patients with ET no sign of subclinical degeneration as seen in PD could be detected and no presymptomatic patient seems could be identified. Therefore patients with ET, at least in the investigated group, did not seem to have a higher predisposition for PD than a normal population, rejecting the discussed connection between ET and PD.

In conclusion [123I]β-CIT and SPECT seems to offer a useful and easily available method of distinguishing essential from parkinsonian tremor and enables an early differential diagnosis of ET and PD. This method furthermore delineates subclinical lesions of the dopaminergic nigrostriatal neurons and can help to identify patients with high risk of developing PD. In the future it might be possible to evaluate the benefit of neuroprotective agents with this technique.

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