[123I]beta-CIT single-photon emission tomography in Parkinson's disease reveals a smaller decline in dopamine transporters with age than controls

Tissingh, G.; Bergmans, P.; Booij, J.; Winogrodzka, A.; Stoof, J.C.; Wolters, E.CH.; van Royen, E.A.

DOI
10.1007/BF01254252

Publication date
1997

Published in
European Journal of Nuclear Medicine

[^{123}I]β-CIT single-photon emission tomography in Parkinson's disease reveals a smaller decline in dopamine transporters with age than in controls

G. Tissingh[1], P. Bergmans[1], J. Booij[2], A. Winogrodzka[1], J.C. Stoof[1], E.C. Wolters[1], E.A. Van Royen[2]

[1] Department of Neurology, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands
[2] Department of Nuclear Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Received 7 June and in revised form 10 June 1997

Abstract. In vivo studies using single-photon emission tomography (SPET) and positron emission tomography have shown an age-related decline in the number of striatal dopamine transporters in healthy subjects. We examined ten healthy subjects and 33 de novo patients with Parkinson's disease (PD) using [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) SPET. A clear age-related loss of dopamine transporters was found in the healthy subjects. In the PD group, controlling for the contribution of disease severity, we found a small (compared with controls) but significant decrease with aging, though only in the ipsilateral regions. This aging effect was especially pronounced in younger patients. We conclude that the use of age-correct SPET data in PD, based on studies with healthy subjects, may lead to an under- or an overestimation of the striatal binding measures.

Key words: Parkinson's disease – Single-photon emission tomography – Dopamine transporter imaging – Aging

Eur J Nucl Med (1997) 24:1171–1174

Introduction

Post-mortem studies have shown an age-related decline in the number of presynaptic striatal dopamine (DA) transporters in healthy subjects, indicating a loss of dopaminergic nigral neurons with increasing age [1–3]. With positron emission tomography (PET) and single-photon emission tomography (SPET), in vivo evaluation of age effects on the integrity of the presynaptic nigrostriatal dopaminergic system has become possible.

In SPET studies using [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT), which has been shown to be sensitive to dopaminergic presynaptic degeneration [4], Van Dyck et al. confirmed in 28 healthy subjects the post-mortem reports on DA transporter loss with increasing age [5].

Two in vivo studies have reported on the effect of aging in Parkinson's disease (PD), without controlling for disease severity and dopaminergic medication. Using ^{11}C-nomifensine PET, Tedroff et al. [6] did not find any significant decline in binding with age (n=6), whereas Marek et al. [7], using [^{123}I]β-CIT SPET, did (n=8).

In this study we investigated possible age effects on the striatal DA transporter binding in healthy subjects and a large group of de novo patients with PD by means of [^{123}I]β-CIT SPET, taking into account the severity of PD.

Materials and methods

Subjects. Thirty-three early and non-medicated PD patients and ten healthy controls were investigated. The patients ranged in age from 32 to 68 years (three were aged 30–39, seven 40–49, 16 50–59, and seven 60–69) and the controls ranged in age from 20 to 65 years (three were 20–29, one 30–39, one 40–49, two 50–59, and three 60–69). PD was diagnosed according to the criteria of the U.K. Parkinson's Disease Society Brain Bank. The severity of the motor signs was assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS). Mean disease duration was 2.5 years (SD=1.3), with a mean Hoehn and Yahr stage of 1.7 (SD=0.6) (Table 1).

The healthy volunteers were free from any neurological or psychiatric disease and were not taking drugs known to affect the dopaminergic system. All subjects gave written informed consent to the research protocol, which was approved by the medical ethical committee of the hospital.

SPET camera and reconstruction. For SPET studies a brain-dedicated camera, the Strichman Medical Equipment 810X system was used. This multidetector camera contains 12 high-resolution focussing collimators, arranged in six pairs opposite to each other. The transaxial resolution of this camera is 7.6 mm full-width at half-maximum of a line source in air, while the axial resolution is 13.5 mm. The energy window was set at 135–190 keV. Data ac-

Correspondence to: G. Tissingh, Academisch Ziekenhuis Vrije Universiteit, Department of Neurology, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

quisition took place in a 128×128 matrix. Reconstruction was always carried out according to the manufacturer's protocol package. The measured concentration of radioactivity was expressed in Strichman Medical Units (SMUs; 1 SMU=100 Bq/ml as specified by the manufacturer).

SPET experiments. The subjects received potassium iodide orally (three doses of 40 mg on the day before imaging and 80 mg just before imaging) in order to block thyroid uptake of free radioactive iodine. [^{123}I]β-CIT (specific activity >185 Bq/nmol; radiochemical purity >99%) was injected intravenously at an approximate dose of 110 MBq. ^{123}I labelling was performed by Amersham Cygne BV (Technical University Eindhoven, The Netherlands), using the trimethylstannyl precursor of β-CIT obtained from Research Biochemicals International (Natick, Mass., USA). SPET image acquisition was performed at 24 h post injection. Slices were acquired during 300-s periods from the orbitromeatal line to the vertex using an interslice distance of 10 mm.

Table 1. Clinical variables and [^{123}I]β-CIT SPET data of patients and controls

	No.	Males/ females	Age (yrs)	UPDRS	Putamen		Caudate		Striatum	
					Ipsi[a]	Contra	Ipsi	Contra	Ipsi	Contra
Patients	33	19/14	52.4	18.0	2.40*	1.68*	4.25*	3.60*	2.95*	2.28*
SD			8.6	6.8	0.78	0.57	1.35	1.24	0.97	0.75
Controls	10	4/6	44.7		6.13	5.99	6.93	6.91	6.28	6.18
SD			16.9		1.97	1.64	1.64	1.51	1.79	1.54

SPET data are expressed as follows: (binding in region of interest−binding in occipital cortex)/binding in occipital cortex. Data are shown as the mean±SD

UPDRS, Unified Parkinson's Disease Rating Scale (motor section); contra, contralateral (contralateral is the side opposite that of initial presentation of motor signs); ipsi, ipsilateral

* Significantly lower compared to the control group (all two-tailed *P* valus <0.005)

[a] In the control group, ipsilateral is arbitrarily assigned to the left side

Table 2. Data of linear regression analysis in patients and controls

Dependent variable	Independent variables	R^2	Sign. *F* *P*<	RC	Beta	Sign. T *P*<
Controls						
Putamen[a]	Age	0.81	0.001		−0.90	0.001
Caudate[a]	Age	0.79	0.001		−0.89	0.001
Striatum[a]	Age	0.84	0.001		−0.91	0.001
Patients						
Putamen contra		0.23	0.05			
	UPDRS			−0.03	−0.38	0.05
	Age			−0.02	−0.28	NS
Putamen ipsi		0.38	0.001			
	UPDRS			−0.04	−0.37	0.05
	Age			−0.04	−0.48	0.01
Caudate contra		0.70	0.0001			
	UPDRS			−0.12	−0.64	0.0001
	Age			−0.04	−0.26	NS
Caudate ipsi		0.48	0.001			
	UPDRS			−0.11	−0.55	0.001
	Age			−0.06	−0.40	0.01
Striatum contra		0.38	0.001			
	UPDRS			−0.06	−0.54	0.001
	Age			−0.02	−0.27	NS
Striatum ipsi		0.46	0.001			
	UPDRS			−0.07	−0.50	0.001
	Age			−0.05	−0.44	0.01

UPDRS, Unified Parkinson's Disease Rating Scale (motor section); contra, contralateral (contralateral is the side opposite that of initial presentation of motor signs); ipsi, ipsilateral; sign., significance; NS, non-significant (*P*>0.05); RC, regression coefficient

[a] Mean (of left and right) ratio of specific to non-specific binding of [^{123}I]β-CIT

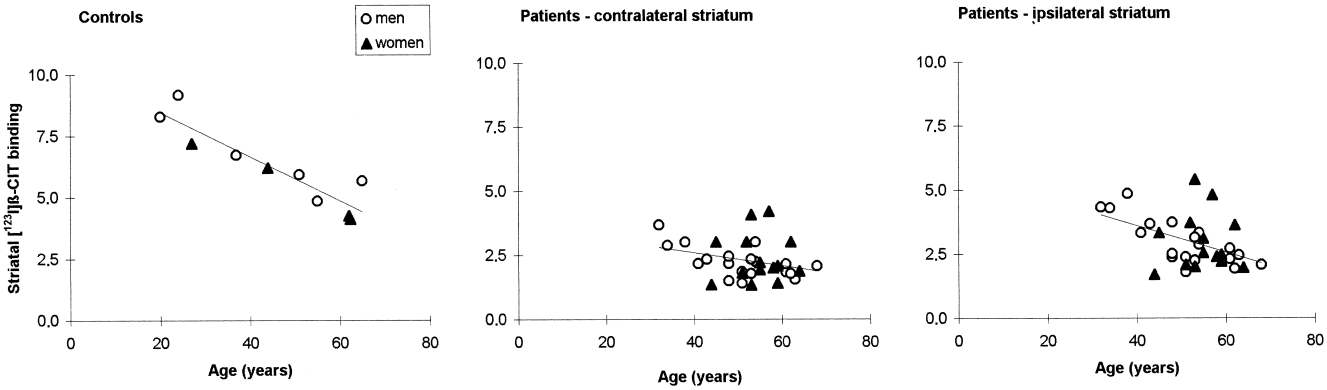

Fig. 1. Striatal [^{123}I]β-CIT binding versus age in ten healthy subjects and 33 de novo patients with PD. Individual data are shown. Regression equations: *controls:* 10.23–0.09×Age; *contralateral striatum:* 4.59–0.06×UPDRS–0.02×Age; *Ipsilateral striatum:* 6.87–0.07×UPDRS–0.05×Age

Data processing. For analysis of striatal [^{123}I]β-CIT binding, the ratio of specific to non-specific binding was calculated by summing two transversal slices representing the most intense striatal binding. A standard region of interest (ROI) template, constructed according to a stereotactic atlas and including regions for putamen, caudate nucleus and occipital cortex, and additional ROIs for the entire striatum, was placed bilaterally on the summed image as previously described [8]. Estimates of specific striatal binding were made by subtracting occipital counts from striatal counts. The ratio of specific to non-specific striatal [^{123}I]β-CIT binding was then calculated, by dividing specific striatal binding by occipital binding [7].

Statistics. Analysis of variance (ANOVA), with age and gender as co-variates, was used to compare the regional SPET measures in the PD patients and healthy controls. The relationship between the binding of [^{123}I]β-CIT and age was examined by linear regression analysis. Significance was assessed at the $P<0.05$ level.

Results

There was no significant difference in age between the patients and the control group (Mann-Whitney test). A significant difference in striatal [^{123}I]β-CIT binding measures between males and females could not be detected either in the patient or in the control group (ANOVA, with age and UPDRS score as co-variates).

The ratios of specific to non-specific [^{123}I]β-CIT binding in all studied regions were significantly lower in the patient group (Table 1).

Linear regression analysis was performed with the ipsilateral and contralateral putamen, caudate nucleus and striatum as dependent variables, and with age and UPDRS motor score as independent variables (Table 2, Fig. 1).

Within the control group, age accounted for a great and significant part of the variance. In the PD group, controlling for the contribution of the severity of PD, age accounted for a smaller, though significant part of the variance in the ipsilateral, but not in the contralateral regions. Furthermore, when the patients were split into three groups with approximately equal class widths [I: 32–45 years (n=7); II: 46–56 years (n=15); III: 57–68 years (n=11)], analyses of variance (UPDRS score as a covariate) showed that the ipsilateral striatal binding measures were higher in group I than in groups II and III (I–II: $P<0.05$, $R^2=0.51$; I–III: $P<0.05$, $R^2=0.41$), but not in group II compared with group III, whereas the contralateral striatal SPET measures were not significantly different between the three subgroups.

Discussion

The results of this study clearly show that [^{123}I]β-CIT binding in the striatum in healthy subjects decreases with age, accounting for a loss of approximately 10% per decade. Although the sample size of the examined healthy controls is rather small, and does not allow an exact estimation of the rate of loss of DA transporters per decade in normal aging, our results are in agreement with human post-mortem observations [1–3, 9] and earlier imaging studies with [^{123}I]β-CIT, finding a loss of 8% per decade [5]. Others have found decreases varying from 3.3% to 7% per decade [10–12]. The use of different ligands and techniques to examine the dopaminergic system, methodological differences, and differences regarding the age range of the control groups might underlie the discrepancies between the reported percentages. For example, Ishikawa et al. [12] found a normal aging effect using [^{123}I]β-CIT-FP SPET, but not with [^{18}F]FDOPA PET in the same subjects. Others [13] showed that the effects of aging may be non-linear, i.e. relatively rapid rates of decline during young adulthood (less than 30 years old).

Interestingly, in 33 de novo PD patients, *controlling for the contribution of disease severity*, we found a small (compared with the controls) though significant influence of age on [^{123}I]β-CIT binding, but only in the ipsilateral regions. This aging effect was also more pronounced in the patients aged 32–45 years than in those

older than 45 years. As mentioned earlier, Marek et al. [7], using [^{123}I]β-CIT, found a significant decline in striatal binding with age in PD patients (*n*=8), while Tedroff et al. [6] failed to find such a decline using ^{11}C-nomifensine (*n*=6). However, in these studies, involving a relatively small number of patients, neither the severity of PD nor the medication was taken into account, which makes it difficult to estimate reliably the contribution of age.

The absence of a significant aging effect in the contralateral regions is probably explained by a more severe, pathological loss of DA transporters compared with the ipsilateral side, masking the age-related loss.

In summary, the present study shows a clear age-related loss of DA transporters in healthy subjects. In de novo PD patients, however, a small decrease with aging was visible only in the ipsilateral striatum, when controlling for disease severity, and this aging effect was especially evident in the younger patients. These findings strongly suggest that the use of age-corrected SPET data, based on studies with healthy controls, may lead to false conclusions regarding the binding capacity and by inference the number of DA transporters. In the case of older patients, the use of such age-correct SPET measures leads to an underestimation of the number of DA transporters, whereas the SPET measures of an early PD patient of age 30 will be less easily recognized as abnormal because of an overestimation of the binding capacity.

Acknowledgements. A. Winogrodzka was supported by a grant from NWO-MW, Den Haag, The Netherlands (number: 49-093).

References

1. Allard P, Marcusson JO. Age-correlated loss of dopamine uptake sites labeled with [^{3}H]GBR-12935 in human putamen. *Neurobiol Aging* 1989; 10: 661–664.
2. Keyser De JD, Ebinger G, Vauquelin T. Age-related changes in the human nigrostriatal dopaminergic systemm. *Ann Neurol* 1990; 27: 157–161.
3. Zelnik N, Angel I, Paul SM, Kleinman JE. Decreased density of human striatal dopamine uptake sites with age. *Eur J Pharmacol* 1986; 126: 175–176.
4. Innis RB, Seibyl JP, Scanley BE, et al. Single photon emission computed tomographic imaging demonstrates loss of striatal dopamine transporters in Parkinson's disease. *Proc Natl Acad Sci USA* 1993; 90: 11965–11969.
5. Van Dyck CH, Seibyl JP, Malison RT, et al. Age-related decline in striatal dopamine transporter binding with iodine-123-β-CIT SPECT. *J Nucl Med* 1995; 36: 1175–1181.
6. Tedroff J, Aquilonius S-M, Hartvig P, Lundqvist H, Gee AG, Uhlin J, Långström B. Monoamine re-uptake sites in the human brain evaluated in vivo by means of ^{11}C-nomifensine and positron emission tomography: the effects of age and Parkinson's disease. *Acta Neurol Scand* 1988; 77: 192–201.
7. Marek KL, Seibyl JP, Zoghbi SS, et al. [^{123}I]β-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. *Neurology* 1996; 46: 231–237.
8. Booij T, Tissingh G, Winogrodzka A, Boer GJ, Stoof JC, Wolters EC, Van Royen EA. Practical benefit of [^{123}I]FP-CIT SPECT in the demonstration of the dopaminergic deficit in Parkinson's disease. *Eur J Nucl Med* 1997; 24: 68–71.
9. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 1991; 114: 2283–2301.
10. Volkow ND, Fowler JS, Wang GJ, et al. Decreased dopamine transporters with age in healthy human subjects. *Ann Neurol* 1994; 36: 237–239.
11. Volkow ND, Ding Y-S, Fowler JS, et al. Dopamine transporters decrease with age. *J Nucl Med* 1996; 37: 554–559.
12. Ishikawa T, Dhawan V, Kazumata K, et al. Comparative nigrostriatal dopaminergic imaging with iodine-123-βCIT-FP/SPECT and fluorine-18-FDOPA/PET. *J Nucl Med* 1996; 37: 1760–1765.
13. Mozley PD, Kim H-J, Gur RC, et al. Iodine-123-IPT SPECT imaging of CNS dopamine transporters: nonlinear effects of normal aging on striatal uptake values. *J Nucl Med* 1996; 37: 1965–1970.