The brain scintiscan with iodine-123-ioflupane to diagnose early Parkinson's disease; seven months follow up. First results in Bulgaria

Elena Piperkova[1],
Roumen Georgiev[2],
Marin Daskalov[3],
Paraskeva Stamenova[3],
Krassimir Katerinski[4],
Maria Beeva[4],
Milka Orozova[3],
Maria Dimitrova[1]

1. *Clinic of Nuclear Medicine and*
2. *Laboratory of Dosimetry and Radiation Protection, National Oncology Centre Hospital, Sofia,Bulgaria*
3. *Clinic of Neurology, Medical University Hospital "Tzaritza Joanna" Sofia, Bulgaria*
4. *Department of Radiology, National Oncology Centre Hospital, Sofia, Bulgaria*

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Correspondence address:
Assoc. Prof. Dr. Elena Piperkova, Clinic of Nuclear Medicine, National Oncology Center Hospital, 6 Plovdivsko pole Str, Sofia 1756, Bulgaria,
E-mail:
elena_piperkova@hotmail.com,
elenapiperkova@yahoo.com

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Abstract

The aim of this study was to evaluate the brain scintiscan images with ^{123}I-ioflupane for the diagnosis of patients with early Parkinson's disease (PD). Sixteen patients were studied, nine males and seven females, aged between 38-81 y (mean age: 64 y). All patients underwent thyroid blocking by oral administration of 120 mg potassium iodide before and 24 h after the intravenous (iv) injection of 110-185 MBq/70 kg patient's weight, of ^{123}I-ioflupane. To check the correct biodistribution of the radiopharmaceutical, whole-body scans were performed at 15 min and 2-3 h after the administration of the radiopharmaceutical. All patients underwent brain single photon emission tomography (SPET) scans on a SPET gamma-camera 3-5 h after ^{123}I-ioflupane administration. To compensate for scatter and to avoid artifacts, the filtering and reconstructing procedures of the images were performed individually for each patient. Brain SPET results were evaluated semi-quantitatively using different indices. The morphology of the nigrostriatum (NS) area was also examined visually. The ^{123}I-ioflupane uptake by the affected nigrostriatum (ANS) was compared to a similar area at the occipital (Occ) brain section and to a similar area at the opposite NS. When the value of ANS/Occ was within the confidence limit of 1.507-1.636 and the value of ANS/NNS was within the limit of 0.755-0.889, PD was diagnosed ($P<0.05$). Thirteen of our patients were diagnosed as having PD and were given L-DOPA treatment. In the remaining patients who had normal scintigraphic and morphologic findings of the NS area, PD was not diagnosed. The interest of this article lies in the following: The correct distribution of the radiopharmaceutical was confirmed by whole body scintiscan. Parameters for better quality of imaging were individually selected for each patient. The morphology of the NS areas, as estimated visually by us, was in accord with the scintigraphic ^{123}I-ioflupane uptake. The diagnosis of PD was clinically confirmed after treatment with L-DOPA after a seven month follow up period. Results from the small number of cases studied showed: 93% sensitivity and maximum specificity for the diagnosis of PD.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with an incidence of one to two cases per 1000 of the population and increasing during the last decade [1]. One in five persons with PD is misdiagnosed [2]. Diagnoses in question include essential tremor (ET), psychogenic parkinsonism, drug-induced parkinsonism, primary dystonia, unspecified gait disorders, result of a stroke, cranio-cerebral trauma, neurotoxins secretion, post-encephalitic changes, cortico-basal degenerations, progressive supranuclear palsy, and multiple system atrophy [3-7]. These diseases have signs and symptoms either normal or only slightly different from PD [8, 9]. A common differential diagnosis of PD is ET where treatment for PD may be harmful [10, 11].

In PD the main histology finding is the progressive degeneration of the nigrostriatum (NS) area and this is accompanied by loss of dopamine delivered to the caudate and putamen [2]. The widely used medical imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) do not visualize the function of the dopamine transporters (DAT) [1,11]. Unfortunately, there is no diagnostic blood test to detect levels of dopamine, and the only diagnostic procedure available is the dopamine transporters brain scan performed with the N-ω-fluoropropyl-2ß-carbomethoxy-3ß-(4-iodophenyl) nortropane labeled with ^{123}I (^{123}I-ioflupane or DaTSCAN, Amersham Health, UK) [12-16].

Single photon emission tomography (SPET) with radiolabeled compounds such as ^{123}I-ioflupane bound to dopamine transporters has been used to diagnose PD [10, 17-23]. This

technique was first practiced in Bulgaria, in our department and we present these results as follows.

Patients and methods

We have studied 16 patients with early PD, 7 women aged between 38 and 81 y (mean age 64 y) and 9 men aged between 52 and 75 y (mean age 63.89 y). Every patient gave his/her prior informed consent for these studies by signing a special form. This study was approved by the Ethics Committee of the Medical University Hospital "Tzaritza Joanna" in Sofia. All PD patients had at least two of the clinical TRAP criteria for PD more common and no family history of PD. Although the DAT agonists and antagonists reacting with postsynaptic DAT receptors do not affect the uptake of ^{123}I-ioflupane or the image quality, treatment with amphetamines, benzotropines or other sedatives was stopped for seven days before the scintiscan. To avoid the ^{123}I uptake in the thyroid gland, the latter was blocked with 120 mg potassium iodide administered per os, two to three h before and 24 h after the intravenous (iv) injection of ^{123}I-ioflupane.

Brain SPET was performed in all patients between third and not later than the fifth hour after the iv injection in the antecubital vein of 111-185 MBq/70 kg body weight of ^{123}I-ioflupane. This drug belongs to a group of compounds, derived from cocaine. To check the correct biodistribution of the radiopharmaceutical, whole-body scans with a speed of 10-12 cm/min were performed at 15 min and at 2-3 h after its injection. The 3D tomographic scans were performed with a single headed gamma-camera (Icon, Diacam, Siemens, Germany) with a low energy, high resolution collimator. For each study 90 projections were completed over 360° and an average of 5 x 10^6 counts was acquired. The image matrix used was 128 x 128 and the slice thickness about 5 mm. To compensate for scatter and to avoid artifacts, the parameters for filtering and three dimensional reconstructions were selected individually for each patient (Fig. 1). Filters most commonly used were Butterworth filter – 0.25 cutoff and order 3, low pass cosine filter – 0.25 cutoff, low pass cosine filter – 0.40 and Shepp Logan – 0.15 cutoff.

The interpretation of the images also included visual evaluation at the transverse and coronal sections of the NS areas as to the shape, symmetry, contour and homogeneity of the distribution of the radiopharmaceutical. A semi-quantitative evaluation of the ratios of the ^{123}I-ioflupane uptake was determined by comparing the counts of similar regions of interest (ROI) at the following areas, separately tested for the right (R) and the left (L) hemisphere: a) at the NS areas versus the occipital (Occ) brain areas (RNS/Occ, LNS/Occ), b) at the considered as PD affected areas of NS (PDANS), PDANS/Occ and c) at the PDANS/normal NS (PDANS/NNS) areas (Fig. 2).

In case PD was confirmed, the patients received treatment with l-DOPA and therapeutic response was clinically followed-up for seven months.

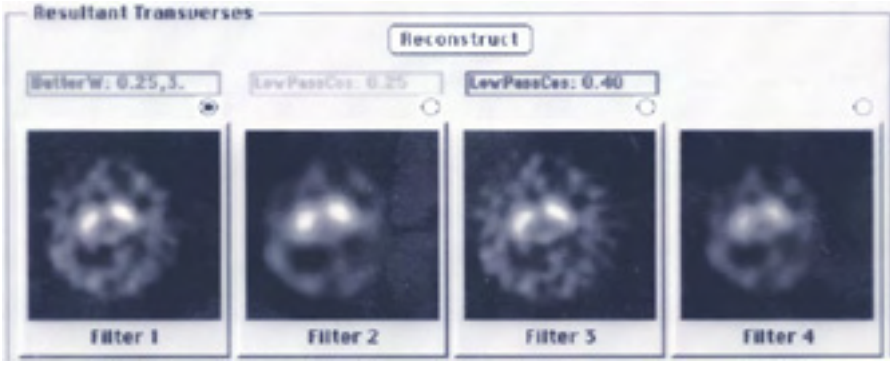


Figure 1. The filtered back projection algorithm with the preferred parameters for image processing of high quality used in this study (different filters left to right: Butterworth filter – 0.25 cutoff and order 3, low pass cosine filter – 0.25 cutoff, low pass cosine filter – 0.40 and SheppLogan – 0.15 cutoff)

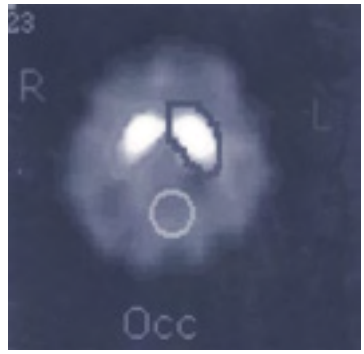
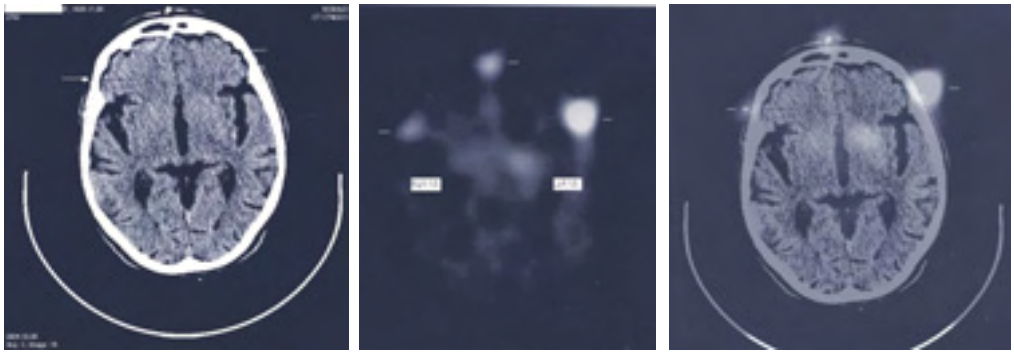


Figure 2. Semi-quantitative indices. The distribution differentiation is based on the calculated ratio of the NS to occipital areas and symmetrically



(a) (b) (c)

Figure 3. Patient No 12 with mild TRAP symptoms on the right lateral view. SPET ^{123}I-ioflupane showed an asymmetric NS area image with decreased uptake of the tracer in the left side: RNS/Occ=2.841, LNS/Occ=1.601 and PDANS/NNS=0.65. Clinical and scintigraphic diagnosis of PD with loss of DAT transporters in the left NS area

Table 1. *^{123}I-ioflupane uptake ratios and clinical data of our patients*

No	Age	RNS/Occ	RNS Image uptake	LNS/Occ	LNS Image uptake	PDANS/Occ	NS/Occ	PDANS/NS	Clinical changes-Body site	Final diagnosis
1	81	2.872	Normal	2.821	Normal	PD -rejected	2.821	1.011	BIL	ET
2	56	1.891	»	1.987	»	PD -rejected	1.987	0.95	»	ET
3	61	1.981	»	1.621	Decreased	1.621	1.981	0.88	R	PD
4	38	1.601	Decreased	1.801*	»	1.608	1.801	0.879	BIL	»
5	64	1.602	»	1.801	Normal	1.602	1.801	0.88	L	»
6	77	1.501	»	1.875	»	1.501	1.875	0.89	»	»
7	71	2.667	Normal	1.511	Decreased	1.511	2.667	0.75	R	»
8	71	2.001	»	2.001	Normal	PD -rejected	2.001	1.001	BIL	ET
9	66	2.824	»	1.521	Decreased	1.521	2.824	0.68	R	PD
10	52	2.781	»	1.63	Mild Decreased	1.651	2.781	0.87	»	»
11	75	1.991	»	1.501	Decreased	1.501	1.991	0.85	»	»
12	68	2.841	»	1.601	»	1.601	2.841	0.65	»	»
13	57	1.621	Decreased	2.381	Normal	1.621	2.381	0.68	L	»
14	72	1.571	»	2.451	»	1.571	2.451	0.63	»	»
15	60	3.001	Normal	1.667	Mild Decreased	1.789	3.001	0.56	R	»
16	54	1.333	Decreased	1.789	Normal	1.333	1.667	0.78	L	»

*This semi-quantitative result was assessed as FN for PD: The normal value 1.801 of the LNS/Occ ratio corresponded with a pathological decreased marker uptake in the left NS image; RNS/Occ and LNS/Occ: Right and left NS and occipital ratio of the 123I-Ioflupane uptake;
PDANS/Occ, NS/Occ and PDANS/NNS: PD affected NS and occipital region ratio; Patients 1-7 were female and 8-16 are male – BIL: bilateral

Table 2. *^{123}I-ioflupane uptake ratios as an indicator for PD*

	PDANS/Occ	NNS/Occ	PDANS/NNS
No of patients	13	16	13
Mean	1.572 ± 0.11	2.304 ± 0.46	0.822 ± 0.12
95% CI of the diff.	1.507-1.636	2.059-2.551	0.755-0.889

P<0.05 for 95% confidence interval (CI) of the difference

Statistics was performed by using SPSS/PC+v.10.0 for Windows with a level of significance for P<0.05 (CI 95%). The sensitivity and the specificity of the method were determined depending on the interpretation of the images, the values of the above indices, and on the therapeutic effect during the follow-up period. Cases with decreased uptake of the radiotracer in the NS, and a non-homogeneous dot line shape of NS corresponding with a good l-DOPA therapeutic response were accepted as true positives (TP) for PD and determined the sensitivity of the study. All cases with normal uptake of the radiotracer in the NS area and a homogeneous comma like shape of NS were referred as true negatives (TN) for PD.

Results

Tables 1 and 2 show the ^{123}I-ioflupane uptake ratios and the clinical data of our patients. In 13 of the 16 patients with early PD the NS had shown a dot like shape, irregular contour and significantly low uptake ratios of the tracer in the NS areas (Fig. 3). In 3 of 16 patients (Nos 1, 2 and 8), brain SPET images showed normal morphologic characteristics and normal bilateral distribution of ^{123}I-ioflupane in both NS areas (Fig. 4a). The whole-body scintiscan (Fig. 4b) showed activity in bilateral NS sections and persisting activity in the lungs and the liver while activity over the thyroid gland was suppressed. Findings in patient No 12 are described in Fig.5.

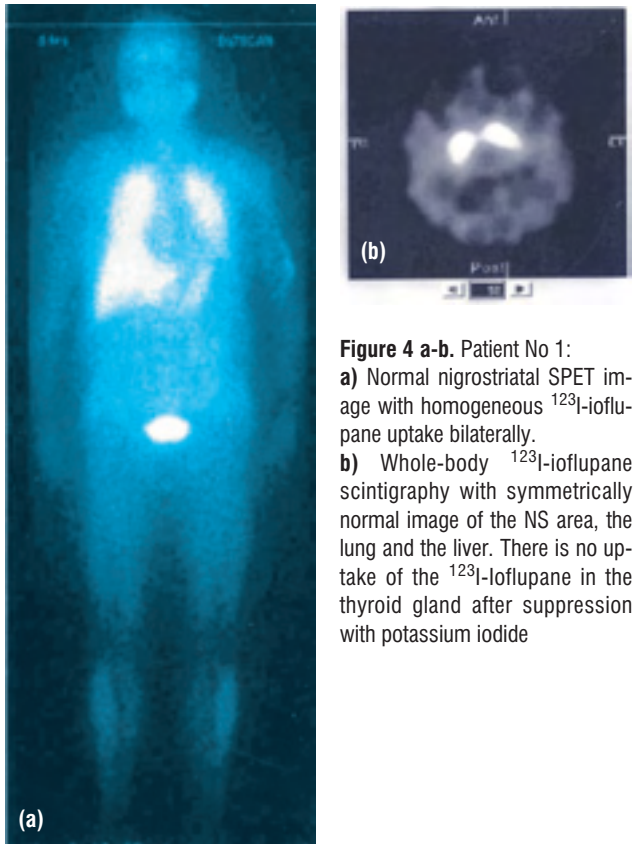


Figure 4 a-b. Patient No 1:
a) Normal nigrostriatal SPET image with homogeneous ^{123}I-ioflupane uptake bilaterally.
b) Whole-body ^{123}I-ioflupane scintigraphy with symmetrically normal image of the NS area, the lung and the liver. There is no uptake of the ^{123}I-Ioflupane in the thyroid gland after suppression with potassium iodide

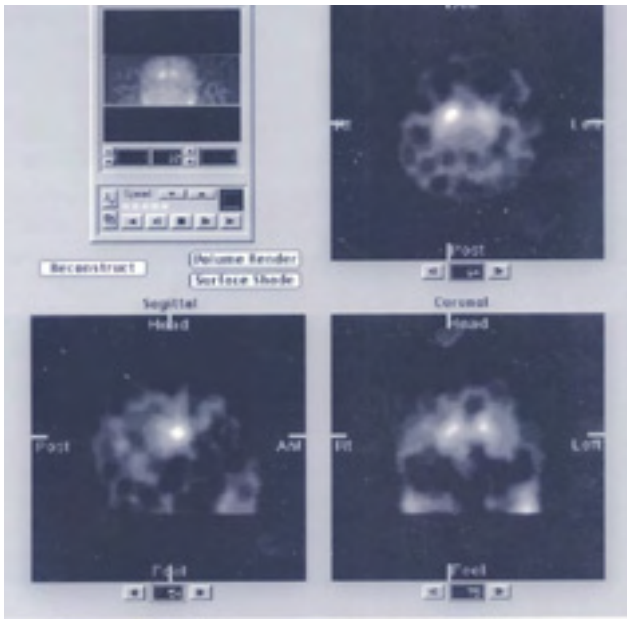


Figure 5. Patient No 12 with mild TRAP symtoms on the right body-side; SPECT ^{123}I-Ioflupane showed an asymmetric nigro-strital area image with decreased uptake of the tracer in the left side. RNS/Occ=2.841, LNS/Occ=1.601 and PDANS/NNS=0.65; a low pass cosine filter with mornalized cut-off frequency of 0.35. Clinical and scintigraphic diagnosis of PD with loss of dopamine transporters in the left nigro-striatal area.

The 13 patients with scintigraphically determined diagnosis of PD were treated and responded to l-DOPA treatment. These patients were followed for up to seven months. The results of this qualitative and semi-quantitative study showed: 93% sensitivity and 100% specificity for the diagnosis of PD.

Discussion

To diagnose early PD is challenging, while many studies have shown that ^{123}I-ioflupane SPET scan, can visualize biochemically defective brain structures and support the diagnosis of PD [3,15,19,20,22]. Catafau et al. (2004) have reported that ^{123}I-ioflupane imaging has changed the clinical management in 72% of their patients [21]. We have diagnosed PD correctly in 13/16 of our patients.

In patient No 4 with bilateral neurological symptoms, the index of RNS/Occ was 1.601, there was abnormal morphology and non-homogeneous decreased uptake of the ^{123}I-ioflupane on the RNS. This result was assessed as a TP, whereas the normal value of the LNS/Occ (1.801) corresponding with an slightly abnormal morphology and non-homogeneous radiopharmaceutical uptake of the LNS was referred as a FN.

Eising et al. (2001) have found in PD a significant correlation of the NS/cerebellar uptake ratios [4]. Jennings et al. (2004) comparing qualitatively the ^{123}I-ioflupane images in patients with early PD after 6 months clinical follow-up, found 25.7% disagreement (92% sensitivity and 30% specificity) whereas comparing quantitatively images, they have found only 8.6% disagreement (92% sensitivity and 100% specificity) [6]. Koranda et al. (2005) have reported that the clinical diagnosis of PD was changed after the ^{123}I-ioflupane scan in 40%-43% of the PD patients [22]. Benamer et al. (2000) have diagnosed PD by ^{123}I-ioflupane with a specificity of 93% and a sensitivity of 97% [10]. From the references mentioned above, we have noticed a sensitivity of 92%-93%, a specificity for the diagnosis of PD of 30%-100% and a percentage of confirming clinical diagnosis of 28%-60%. Results in our study, although performed in a small number of patients, have shown sensitivity of 93%, specificity of 100% and confirmation of the clinical diagnosis of PD in 81% of the patients studied.

According to our studies, PD was diagnosed when the indices for PDANS/NNS were at the confidence limit of 0.755-0.889 and when the indices for PDANS/Occ were at the confidence limit of 1.507-1.636 ($P<0.05$). If patients with movement impairments and clinically diagnosed as having early PD, had the index of NS/Occ within the confidence limit of 2.059-2.551, the diagnosis of PD was rejected. The morphology of the NS areas always complied with the ^{123}I-ioflupane findings. This compliance indicates the importance of testing the morphology of the NS areas as a critical sign for the diagnosis of PD. Whole body scintiscan confirmed the biodistribution of the ^{123}I-ioflupane. The seven month follow up of the 13 positive for PD patients with a good l-DOPA therapeutic response confirmed the correct diagnosis of the ^{123}I-ioflupane scan.

In conclusion, this semi-quantitative functional image method with ^{123}I-ioflupane is very sensitive and specific for the diagnosis of PD. The morphology features of the NS areas and the follow up of these patients support the importance of the above scintiscan.

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