123I-FP-CIT brain SPECT (DaTSCAN) imaging in the diagnosis of patients with movement disorders – First results

SPECT scintigrafija mozga korišćenjem 123I-FP-CIT (DaTSCAN) u dijagnostici bolesnika sa poremećajem pokreta – prvi rezultati

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Abstract

Background/Aim. 123I-FP-CIT brain single-photon emission computed tomography (SPECT), DaTSCAN imaging, offers a possibility to study structural and biochemical integrity of presinaptic dopaminergic neurotransmitter system. The aim of this study was to evaluate the usefulness of 123I-FP-CIT brain SPECT scintigraphy in patients with extrapyramidal diseases. **Methods.** Fifteen patients (8 males and 7 females), aged 26–81 years, presenting with extrapyramidal symptoms entered the study. Out of them, 7 patients were diagnosed with definite clinical form of idiopathic Parkinson's disease (PD) or clinical probable for PD clinical stage 2–4 using the Hoehn&Yahr scale (H&Y); 6 patients were with atypical parkinsonism (AP), 1 patient with essential, and 1 with psychogenic tremor. SPECT was performed 180 min after injection of 185 MBq 123I-FP-CIT using a dual head Gamma camera. Sixty four one minutes' frames were acquired using a noncircular rotation mode into a 128 × 128 image matrix. Transverse slices were reconstructed using a 0.6 order Butterworth filter. Visual interpretation was based on striatal uptake, left to right asymmetry and substructures most affected. The ratio of binding for the entire striatum, caudate and putamen to nonspecific binding in occipital cortex was calculated. SPECT findings were categorized as normal and abnormal (incipient, moderate and severe presinaptic deficit). **Results.** 123I-FP-CIT uptake was reduced in the striatum of 6/7 patients with PD and 5/6 patients with AP. Two patients with PD and AP showed a negative finding. The remaining 2 negative results were obtained in the patients diagnosed with essential tremor and psychogenic tremor. The mean striato-occipital ratio (SDR) of the most affected side was lower in the patients with PD. **Conclusion.** Our first results confirm the usefulness of 123I-FP-CIT brain SPECT in differential diagnosis of extrapyramidal diseases.

Key words:
parkinsonian disorders; parkinson disease; diagnosis, differential; tomography, emission-computed, single photon; radionuclide imaging.

Apstrakt

Uvod/Cilj. Scintigrafija mozga pomoću 123I-FP-CIT (DaTSCAN) tehnikom jednofotonske emisione komjuterizovane tomografije (SPECT), omogućava ispitivanje strukturnog i biohemijskog integriteta presinaptičkog dopaminergičkog neurotransmiterskog sistema. Cilj ovog rada bio je procena doprinosa 123I-FP-CIT SPECT scintigrafije mozga kod bolesnika sa ekstrapiramidnim poremećajima. **Metode.** Ispitivanjem je bilo obuhvaćeno 15 bolesnika (osam muškaraca i sedam žena), starosti 26–81 godine, sa kliničkim manifestacijama ekstrapiramidnog sindroma. Od ukupnog broja bolesnika, kod sedam inicijalno je postavljena dijagnoza Parkinsonove bolesti (PD) ili sumnja na PD, kod šest bolesnika dijagnoza atipičnog parkinsonizma (AP), a kod dvoje dijagnoza esencijalnog, odnosno psihogenog tremora. Snimanje mozga rađeno je SPECT tehnikom, dvoglavom gama kamerom, 180 min posle davanja obeleživačke doze 123I-FP-CIT-a aktivnosti 185 MBq. Akvizicija 64 jednominutna frema vršena je po necirkularnoj orbiti u matrici 128 × 128. Transverzalni preseci su rekonstruisani korišćenjem 0,6-rednog Butterworth filtera. Vizuelna interpretacija nalaza bazirana je na nakupljanju radiofarmaka u strijatumu, asimetriji vezivanja levo/desno i najzahvaćenijim supstrukturama. Indeks vezivanja je računat na osnovu odnosa nakupljanja u strijatumu, kaudatumu i putamenu i nespecifičnog nakupljanja u okcipitalnom korteksu. Nalazi SPECT-a su kategorizovani kao normalni i patološki (početni, umereni i izraženi presinaptički deficit). **Rezultati.** Nakupljanje 123I-FP-CIT bilo je oslabljeno u regiji strijatuma kod šest od sedam bolesnika sa

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pouzdanom dijagnozom ili sumnjom na PD, kao i kod pet od šest bolesnika sa AP. Dva negativna nalaza dobijena su kod dve bolesnice sa PD i AP. Preostala dva negativna nalaza dobijena su kod dva bolesnika sa esencijalnim, odnosno psihogenim tremorom. Srednja vrednost strijato-okcipitalnog indeksa vezivanja na zahvaćenoj strani mozga bila je niža kod bolesnika sa PD. **Zaključak.** Naši prvi rezultati potvrđuju doprinos ^{123}I-FP-CIT SPECT scintigrafije mozga u diferencijalnoj dijagnostici bolesnika sa ekstrapiramidnim poremećajima.

Ključne reči:
parkinsonov sindrom; parkinsonova bolest; dijagnoza, diferencijalna; tomografija, komjuterizovana, emisiona, jednofotonska; scintigrafija.

Introduction

The term Parkinson's disease refers to a group of neurodegenerative conditions considered to primarily come from abnormalities of basal ganglia function. PD is one of the most common neurodegenerative diseases affecting about 329 per 100 000 people (age-adjusted prevalence rate) [1]. Although the etiology of PD is not completely understood, the condition probably results from a combination of polygenic inheritance, environmental exposures, and gene–environment interactions. Data has implicated mitochondrial dysfunction, oxidative damage, aberrant protein aggregation, and deficits in ubiquitin-mediated protein degradation as playing key roles in the etiopathogenesis of PD [2–4]. In PD degeneration of dopaminergic neurons and their projection to the striatum is a slowly evolving process that may take decades to develop. In most cases the diagnosis of PD is straightforward when cardinal clinical signs and symptoms as bradykinesia, rigidity, and resting tremor are present [5]. However, these main features of PD are shared, at least in part by essential tremor, multisystem atrophy, progressive supranuclear palsy, vascular parkinsonism, dementia with Lewy bodies, corticobasal degeneration, Alzheimer's disease, and drug-induced parkinsonism. Besides, delineating PD from the above mentioned parkinsonian disorders distinguishing PD from normality can also be difficult, especially in early stage of the disease [6].

A reliable test to diagnose PD is important for at least two reasons. Prognosis and management of PD and other parkinsonian disorders differ considerably [7], and an objective disease marker would facilitate the development of neuroprotective therapies [8]. Several procedures have been proposed to diagnose PD: functional imaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT), transcranial sonography, olfactory and neuropsychological tests, biomarkers and DNA tests [9–12].

Imaging of the dopaminergic system with SPECT is used since radiopharmaceuticals for imaging the presynaptic dopamine transporter, as well as the dopamine D2 receptors became commercially available.

Dopamine transporters are localized on dopaminergic nerve endings and are lost in the process of degeneration in PD. They can be used as markers for the integrity or for the degree of loss of dopaminergic nerve endings. The cocaine derivative ^{123}I-labeled N-(3-fluoropropyl)-2ß-carbomethoxy-3ß-(4-iodophenyl)nortropane (FP-CIT) (DaTSCAN®, GE Healthcare) binds with high affinity to dopamine reuptake sites in the striatum and can be used to visualize dopaminergic nerve terminals *in vivo* in the human brain. The nuclear medicine method – brain SPECT with ^{123}I-FP-CIT is a valuable tool for discriminating neurodegenerative parkinsonian syndromes with an associated presynaptic dopaminergic deficit from diseases without presynaptic neurodegeneration [13]. SPECT with ^{123}I-FP-CIT is a sensitive marker of dopaminergic degeneration, and the degree of striatal binding reduction in PD correlates with disease severity [14, 15]. Dopamine transporter imaging offers the prospect of a quick, objective method to confirm or exclude presynaptic parkinsonism (PD) in inconclusive cases [16].

The aim of the study was to evaluate our first results with ^{123}I-FP-CIT SPECT in patients with extrapyramidal diseases.

Methods

Since January 2009, 15 patients (age range 26–81, median 67 years) with clinical findings suggestive of extrapyramidal disorders have been referred to our institution for ^{123}I-FP-CIT brain SPECT. All parkinsonian patients fulfilled clinical diagnostic criteria for PD [5]. The disease staging (modified Hoehn &Yahr score [17]) was given at the time of SPECT examination all but one patient with PD and atypical parkinsonism (AP) (range 1.00–4.00, mean 2.70 ± 1.07 standard deviation).

Thyroid uptake was blocked before the scan by administration of 400 mg of perhlorate at least 30 min prior to the injection. All subjects received 150–185 MBq (4–5 mCi) of ^{123}I-FP-CIT in slow intravenous injection. During the acquisition, the patient's head was fixed in with elastic band to minimize motion artifacts.

Acquisition started between 3 and 4 hours after intravenous injection of commercially available radiopharmaceutical ^{123}I-FP CIT (DaTSCAN®, GE Healthcare). Data were acquired with a double-head camera (Vertex, Adac) using low-energy-general purpose collimators, in 64 × 64 matrix size. Sixty four projections were acquired at 60 s per view with the camera heads following a non-circular orbit, resulting in a total scan time of 32 min. Total brain count of more than 1.5 million was achieved in all examinations. SPECT data were reconstructed by back projection filtered with a Butterworth filter (0.6 cut of value, order 8).

SPECT images were interpreted visually and semiquantitatively using region of interest techniques to assess specific ^{123}I-FP-CIT binding in striatum and striatal subregiones.

The findings were classified as normal if symmetric intense tracer uptake in striatum and striatal subregiones presented. Abnormal findings were categorized as incipient, moderate and severe presinaptic deficit. Incipient presinaptic deficit was defined as asymmetrical one-sided slightly re-

duced putamen uptake. Moderate presinaptic deficit was defined as reduction in specific/nonspecific tracer binding and poor visualization of putamen in both sides, and, finally, severe presinaptic deficit as significant reduction of specific binding resulting in vizualisation of background activity through the brain hemispheres.

For analysis of striatal ^{123}I-FP-CIT binding, 3 transaxial slices representing the most intense striatal binding were summed. Irregular regions of interest were constructed manually in areas corresponding to the right and left striatum, caudate, and putamen. Irregular regions of interest were also drawn in area corresponding to the occipital cortex (Figure 1).

The mean specific basal ganglia binding was calculated from the mean counts per pixel in the whole striatum, cau-

date nucleus, and putamen (specific binding), dividing the results by the mean counts per pixel in the occipital cortex (nonspecific binding). The ratios expressed as mean ± standard deviation, were compared between the patients.

Results

Subject demographic data are given in Table 1. Four patients had normal striatal ^{123}I-FP-CIT binding (Figure 2) with no significant differences in striatal or subregional binding ratios. Eleven patients had abnormal ^{123}I-FP-CIT SPECT findings – assigned as incipient, moderate and severe presinaptic deficit was found in 2, 5 and 4 patients, respectively (Figures 3 and 4). Subanalyses showed diminished
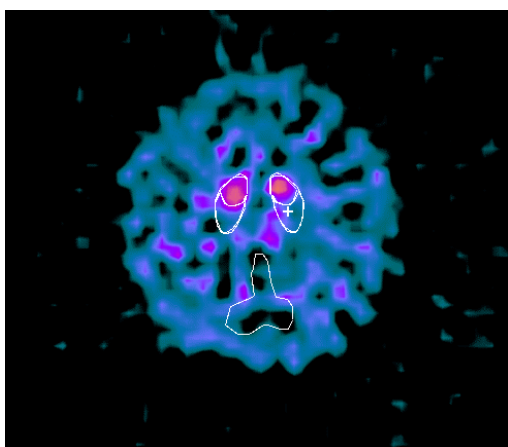

Fig. 1 – Irregular regions of interest were constructed manually in areas corresponding to the right and left striatum, caudatum, putamen, and occipital cortex
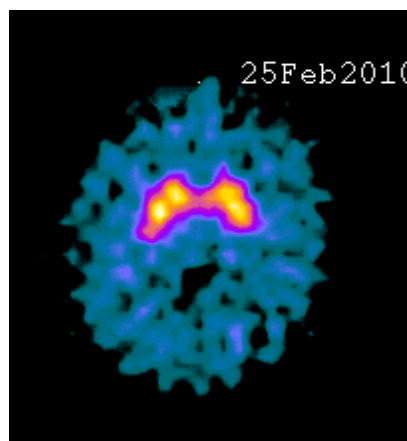

Fig. 2 – Normal ^{123}I-FP-CIT SPECT in patient with essential tremor

Table 1

Demographic and clinical characteristics of patients with Parkinson`s disease (PD)

Parameter	PD	AP	ET/PT
Patients number	7	6	2
Age (year) ($\bar{x} \pm$ SD)	66.7 ± 8.8	59.8 ± 20.3	65.0 ± 21.2
Sex (M/F)	3/4	4/2	1/1
Modified H&Y score	2.42 ± 0.93	3.10 ± 1.24*	–

*1 patient missing; AP – atypical parkinsonism, ET – essential tremor, PT – psyhogenic tremor, H&Y score – Hoehn&Yahr score
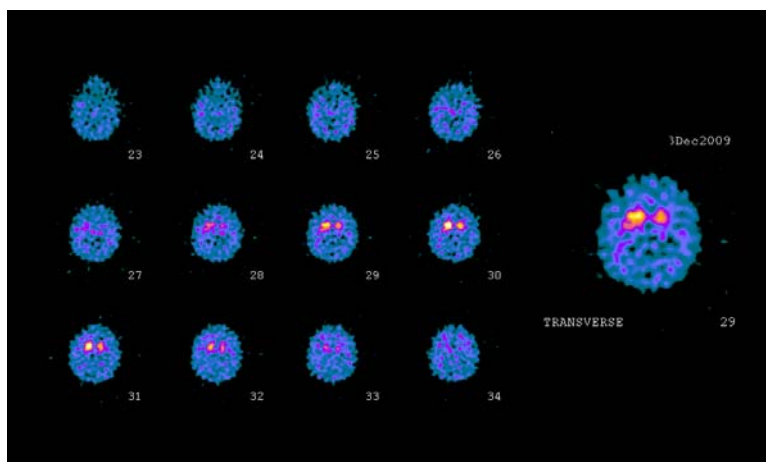

Fig. 3 – ^{123}I-FP-CIT SPECT interpreted as moderate presinaptic dopaminergic deficit in patient with Parkinson`s disease (clinical stage 2.0 H&Y)
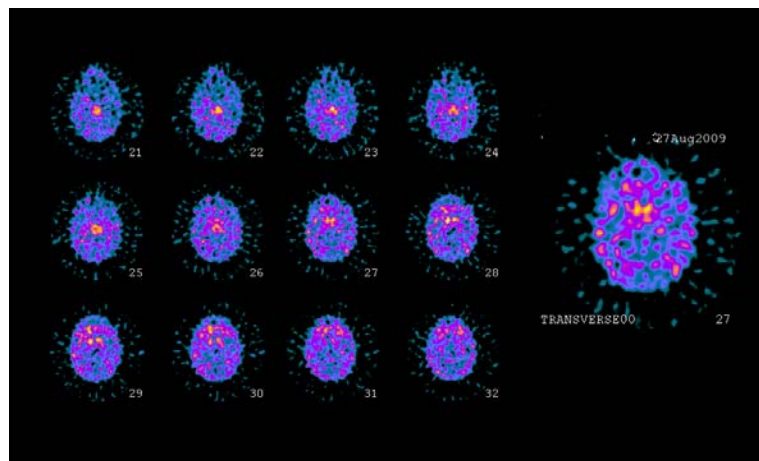
Fig. 4 – ^{123}I-FP-CIT SPECT interpreted as severe presinaptic dopaminergic deficit in patient initially diagnosed with atypical parkinsonism (clinical stage 4.0 H&Y)

binding in the caudate (2.15 ± 0.56 and 2.16 ± 0.56 for the right and left caudate, respectively), diminished binding in the putamen (1.82 ± 0.32 and 1.86 ± 0.47 for the right and left putamen, respectively).

^{123}I-FP-CIT binding ratios in the whole striatum, the caudate, and the putamen are presented in Table 2.

pathic PD either clinical probable for PD. All but one patient had a pathological ^{123}I-FP-CIT SPECT finding graded as moderate to severe presinaptic dopaminergic deficit. Normal ^{123}I-FP-CIT SPECT findings was obtained in a 72-year old woman diagnosed with PD in early stage (H&Y = 2). Rather than the false negative result, the pausible explanation may

Table 2

Specific ^{123}I-FP-CIT uptake ratio observed in striatum, caudatum, and putamen of patients with Parkinson`s disease (PD)

Patient N°	Clinical diagnosis	SPECT visually estimated*	Striatal region					
			Striatum		Caudatum		Putamen	
			R	L	R	L	R	L
1	PD	3	1.09	1.15	1.26	1.36	1.3	1.0
2	PD	1	1.77	1.72	2.04	2.01	1.77	1.49
3	ET	1	3.72	3.72	4.24	4.8	4.45	3.56
4	AP	5	1.65	1.52	1.79	1.71	1.85	1.48
5	AP	3	1.87	2.04	2.54	2.58	2.07	2.17
6	PD	2	1.89	2.16	2.93	3.04	1.89	2.28
7	PD	3	1.97	1.71	2.37	1.94	1.58	1.52
8	AP	3	2.5	2.15	2.5	2.54	2.46	1.91
9	PD	5	1.97	1.73	1.97	2.05	1.6	1.5
10	PT	1	2.37	2.4	2.42	2.82	2.42	2.47
11	PD	5	1.38	1.6	1.3	1.52	1.47	2.72
12	PD	3	2.12	2.24	2.47	2.47	1.92	2.05
13	AP	1	2.62	2.39	3.31	3.33	2.88	2.07
14	AP	2	2.27	2.24	2.77	2.85	2.01	2.05
15	AP	5	1.72	1.81	1.83	1.75	1.94	1.88
x̄ ± SD			2.06 ± 0.62	2.03 ± 0.58	2.38 ± 0.76	2.45 ± 0.87	2.10 ± 0.71	2.01 ± 0.61

AP – atypical parkinsonism, ET – essential tremor, PT – psyhogenic tremor, R – right, L – left,
*1 – normal DaTSCAN, 2 – incipient presynaptic deficit, 3 – moderate presynaptic deficit, 5 – severe presynaptic deficit

Discussion

There is no confirmatory test for PD except the hystopathological one. Although idiopathic PD represents the most prevalent form of Parkinson′s syndrome, at early stages of disease it could be difficult to differentiate idiopathic PD from other forms of parkinsonism solely on clinical grounds, taking in considerations that share, at least partialy, similar symptoms such as tremor, bradykinesia, rigidity, gait disturbance, speech or swallowing difficulties and autonomic dysfunction [18].

Out of 15 patients enroled in our study, seven were already diagnosed patients with clinical definite form of idio-

be that the patient initially diagnosed as having PD actually have another disorder; moreover, taking into account that it occurs in 10%–25% of PD cases when reviewed pathologically [19]. In addition, approximately 10% of patients diagnosed clinically with early PD have normal dopaminergic functional imaging (Scans Without Evidence of Dopaminergic Deficit [SWEDDs]) [20, 21] .The diagnosis in these patients has been debated: is it early PD, some previously unrecognized form of PD, or not PD at all? A recent study analysing clinical details including non-motor symptoms in 25 tremulous SWEDDs patients in comparison with 25 tremordominant PD patients showed that underlying pathophysio-

logy of SWEDDs differs from PD but has similarities with primary dystonia [22]. Distinguishing these patients from PD is important, cause the correct diagnosis will help avoid inappropriate PD drug treatments. Study comparing DaT-SPECT results in autopsy findings in 25 patients with parkinsonian disorders suggests that DaT-SPECT can reliably document dopaminergic degeneration in Lewy body disorders [23].

The mean striatal FP-CIT binding was decreased in our patients already diagnosed as having PD (1.79 ± 0.36, 1.81 ± 0.35 for the right and left striatum, respectively), concordantly with literature data. Striatal ^{123}I-FP-CIT binding is reduced in PD in proportion to disease severity [14, 15]. Studies with 6-18F-fluoro-L-dopa PET suggest that the disease process in PD first affects the posterior putamen, followed by the anterior putamen and the caudate nucleus [24]. Our results showed that the putamen ^{123}I-FP-CIT binding was markedly reduced in subgroup of PD patients (1.73 ± 0.40, 1.76 ± 0.39 for the right and left putamen, respectively) *vs* the mean putamen binding (2.10 ± 0.71, 2.01 ± 0.61 for the right and left putamen, respectively) (Table 2).

Clinical rating scales, H&Y and the Unified Parkinson`s Disease Rating Scale (UPDRS) scores, have a high sensitivity and specificity for the clinical diagnosis of PD [25]. These rating scales, however, are more difficult to apply in patients with atypical parkinsonism. The clinical diagnosis is most difficult early in the disease when the signs and symptoms are quite subtle. Moreover, symptoms in PD become apparent only after a critical level of cell loss – the "symptom threshold" [26] – requiring a loss of approximately 80% of dopamine innervation.

We found interesting a case of 50-year-old woman with atypical parkinsonian syndrome and a ^{123}I-FP-CIT SPECT finding suggestive for PD performed in another institution 9 months ago. For the reason she clinically was not likely to be diagnosed with PD, we obtained a control scan. The typical abnormal finding consisting for the severe presinaptic deficit in PD was shown. Our finding contributed to clinical characterization of patient, which is of importance in therapy selection and prognosis.

Several studies on patients with known PD in early stage showed the ability to differentiate between PD and normally with 100% specificity. In distinguishing Alzheimer disease from Dementia Lewy body, *in vivo* findings of presynaptic dopaminergic imaging correlated well with neuropathological findings at autopsy, suggesting a remarkable sensitivity of 77%–88% and a specificity of 87.9%–100.0% [27–29].

According to the results of a meta-analysis of the literature data on diagnostic accuracy of SPECT in parkinsonian syndromes [30], SPECT with presynaptic radiotracers are highly accurate in differentiation between patients with

PD and essential tremor. We had only two patients with clinical diagnosis suggestive to essential or psychogenic tremor and we obtained normal results in both of them. Normal SPECT FP-CIT finding enabled clinicians to exclude a neurodegenerative parkinsonian syndrome. The use of ^{123}I-FP-CIT SPECT can prove or exclude high sensitivity nigrostriatal dysfunction in cases of monosymptomatic tremor (dystonic tremor, essential tremor, Parkinson tremor) and facilitates early and accurate diagnosis. Furthermore, a normal ^{123}I-FP-CIT SPECT is helpful in supporting a diagnosis of drug-induced, psychogenic and vascular parkinsonism by excluding underlying true nigrostriatal dysfunction [31, 32].

Recent study of Antonioni et al. [33] reported that ^{123}I-FP-SPECT is likely to be regarded as economically advantageous to differentiate essential tremor from PD, increasing time on potentially beneficial therapy at a lower cost to healthcare system.

In addition, the study comparing the scanning techniques ^{123}I-FP-CIT and F-DOPA (positron emmision tomography tehnique) reported the sensitivity of 91% for both and specificity of 100% and 90% for ^{123}I-FP-CIT and F-DOPA, respectively, in the diagnosis of presynaptic dopaminergic deficits in early phases of PD [34].

A limitation of our study is that we did not include the healthy volunteer control group because of the absence of validated control population for ^{123}I-FP-CIT. In addition, manually constructed regions of interest may be the source of errors, as well. Using voxel-based analysis with anatomic standardization or validated an automated technique combining perfusion and ^{123}I-FP-CIT SPECT may contribute in the differential diagnosis of parkinsonism under clinical circumstances [35].

Conclusion

Imaging presynaptic dopamine transporter as an important diagnostic tool for patients with parkinsonian syndromes has become a routine clinical procedure in nuclear medicine departments in Europe. The technique is relatively accurate to differentiate patients with PD in an early phase from healthy one, patients with PD from those with essential tremor, and PD from vascular parkinsonism.

Based on the first 15 ^{123}I-FP-CIT SPECT studies performed in our Institute, we showed that ^{123}I-FP-CIT SPECT studies provide useful information used to confirm or exclude PD leading to change the diagnosis and patient management. ^{123}I-FP-CIT SPECT can therefore be considered useful tool in the diagnosis of patients with atypical clinical presentation of PD.

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