Dopamine transporter imaging ^{123}I-FP-CIT (DaTSCAN) SPET in differential diagnosis of dopa-responsive dystonia and young-onset Parkinson's disease

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Abstract

Dopa-responsive dystonia (DRD) is a genetic disorder characterized by childhood onset dystonia, dominant inheritance, diurnal symptoms fluctuation and positive levodopa response. Adult-onset DRD is frequently combined with parkinsonism and can be mistaken with young onset Parkinson's disease (YOPD). Both conditions are caused by dopamine deficiency, due to nigral cells' loss in YOPD, and due to enzymatic defects in dopamine synthesis in DRD. Single photon emission tomography (SPET) with ^{123}I-*N*--fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane (^{123}I-FP-CIT)-DaTSCAN is a sensitive neuroimaging method for the assessment of nigrostriatal dopaminergic system integrity and degeneration. *Our aim* was to evaluate the usefulness of ^{123}I-FP-CIT(DaTSCAN) SPET in the differential diagnosis of DRD and YOPD in clinical practice. *Brain SPET with ^{123}I-FP-CIT* was performed in 13 patients (7 males, 6 females), age 20-58 years, with mean age of onset of their disease, 29 years, eleven patients with early onset parkinsonian symptoms and 2 with genetically proved DRD. The images were evaluated by visual and semiquantitative analyses (ROI). The ratio of specific-striatal to non specific-occipital binding was calculated. *Ten out of 11 patients with YOPD* had decreased accumulation of DaTSCAN in striatum, especially in putamen, that is typical findings for Parkinson's disease. In three patients DaTSCAN was normal with symmetric tracer uptake in both striata, caudate nucleus and putamen and the diagnosis of DRD was suspected. Two patients with initial dystonic symptoms and genetically proved DRD had normal DaTSCAN. In one patient after normal DaTSCAN findings the initial diagnosis of YOPD was changed to the diagnosis of DRD. Region of interest (ROI) analyses have shown significantly lower^{123}I-FP-CIT binding ratios in YOPD than in DRD in all 3 regions of interest: striatum (1.95±0.32) vs (2.76±0.10) P<0.001, putamen (1.76±0.25) vs (2.84±0.14) P<0.0001 and caudate nucleus (2.37±0.51) vs (3.27±0.14) P<0.01. In *conclusion,* our results indicate that DaTSCAN is an objective neuroimaging method able to distinguisch neurodegenerative disease YOPD from DRD and clarify a clinical dilemma, which is important for the treatment, prognosis and genetic counseling of patients and their families.

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Introduction

Dopa-responsive dystonia (DRD) is a genetic disorder characterized by childhood onset dystonia, dominant inheritance, diurnal symptoms fluctuation and positive levodopa response [1-3]. This disease belongs to a group of primary dystonia and typically presents as a dystonic gait disorder usually appearing at early childhood. However, when DRD appears in adults, it usually presents as Parkinsonism and can be mistaken for Parkinson's disease. The features of Parkinsonism include slowness of movements, instability or lack of balance, and less commonly tremor of the hands at rest. Young-onset Parkinson's disease (YOPD) is defined by an onset between 21 and 40 years of age or even up to the age of 50 years according to some authors [4]. Dystonia is a frequent symptom, common at onset in YOPD, and most frequently involves the lower limbs. Clinical symptoms and signs overlap and differential diagnosis between DRD and YOPD is difficult especially at the early stage of the disease. Both conditions have metabolic dopamine deficiency in the nigrostriatal system. Their difference is due to the presence or absence of nigral cells loss. Pathological degenerative nigral cells loss is found in YOPD, while enzymatic defects in dopamine synthesis in the dopaminergic neurons, without cell death, are present in DRD [5]. Mutations have been found in the GTP cyclohydrolase I (GCH I) in more than 50% of the patients with autosomal dominant inherited DRD and tyrosine hydroxylase (TH) genes in autosomal recesessive DRD [3, 6-9].

Single photon emission tomography (SPET) with dopamine transporter (DAT) ligands like ^{123}I-beta-carbomethoxy-3b- (4-iodophenyl) nortropane (^{123}I-beta CIT), ^{99m}Tc-TRODAT, ^{123}I-ioflupane-^{123}I-*N*--fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane (^{123}I

FP-CIT-(DaTSCAN) is a sensitive neuroimaging method for the assessment of nigrostriatal dopaminergic system integrity and degeneration. The loss of neurons leads to decreased concentration in presynaptic DAT and decreased uptake of ^{123}I-FP-CIT in striatum in YOPD [10-15]. Patients with DRD have selective nigrostriatal dopamine deficiency without neuronal loss caused by genetic defects in dopamine synthesis, and DAT imaging is normal [11, 15-18]. Both diseases are rare and L-dopa responsive. On the other hand, prognosis and the long-term L-dopa benefit differ significantly. Dopa responsive dystonia has an excellent response to long-term levo-dopa treatment without development of side-effects [19]. Clarification of the diagnosis is important for treatment, prognosis and genetic counseling of patients and families. A few reports with limited number of patients, have indicated the potential value of brain SPET with different DAT binding tracers (^{123}I-beta-CIT, ^{99m}Tc-TRODAT, ^{123}I-FP-CIT) and positron emission tomography (PET) with DAT tracer or ^{18}F-6-fluorodopa for the assessment of dopaminergic system integrity in YOPD and DRD and suggested the need for further investigations [16-18, 20-23]. Therefore, the aim of this study was to evaluate the usefulness of ^{123}I-FP-CIT SPET in the differential diagnosis of DRD and YOPD adult patients in our clinical practice.

Materials and methods

Thirteen patients (7 males, 6 females), age 20-58 years, with mean age of onset of the diseases of 29 years, from Department for movement disorders and neurodegenerative diseases, Clinic for Neurology, Clinical Centre of Serbia, were referred to brain SPET using ^{123}I-ioflupane-FP-CIT (DaTSCAN) in order to clarify diagnosis of YOPD and DRD. The study protocol was approved by the Ethics Committee of our Center and written inform consent was obtained from all patients. All subjects underwent detailed neurological examinations by a movement disorders specialist. There were 11 patients with early onset of parkinsonian symptoms and 2 patients with DRD. Young-onset Parkinson's disease were diagnosed according to the UK Brain Bank criteria. In all patients we excluded the following secondary causes of parkinsonism: Wilson's disease, drug induced parkinsonism, and structural causes. The results of structural imaging (such as computed tomography (CT) and magnetic resonance imaging (MRI)) were normal in all patients. Wilson's disease was excluded by measurement of serum copper, ceruloplasmin, urinary 24h copper excretion, and assesment for Kayser-Fleisher rings. No patient had a history of neuroleptic or antiemetic drug use. Genetic testing for DRD was performed in two patients (cases 12, 13), using standard protocol which included polymerase chain reaction (PCR) amplification and deoxyribonucleic acid (DNA) sequencing according to the method of Senger and autoradiography.

Brain SPET

Functional imaging SPET using ^{123}I-ioflupane-FP-CIT (DaTSCAN) was performed in all patients. Patients received premedication 1h before the radiotracer injection in order to block the uptake of free ^{123}I in the thyroid gland. Brain SPET was performed 3-5h after intravenous injection of 145-185MBq of ^{123}I-ioflupane-FP-CIT (DaTSCAN, Amersham, GE Healthcare). Image acquisition was carried out with a Mediso

[^{123}I]FP-CIT-DATSCAN SPET

YOPD

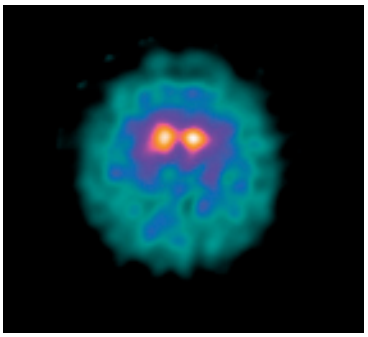

Figure 1. Bilaterally decreased uptake in the striatum, predominantly in putamen L>R (case 7).

YOPD

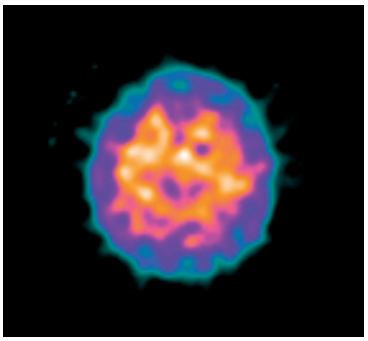

Figure 2. Decreased striatal uptake with increased uptake out of striatum-advanced disease (case 9).

DRD

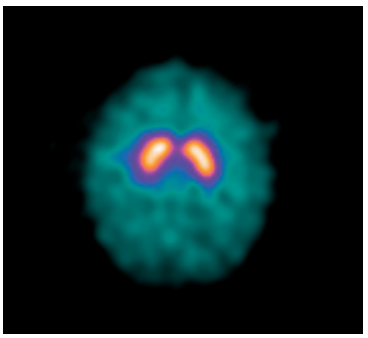

Figure 3. Symmetric tracer uptake in the striatum-normal DAT scan (case 11).

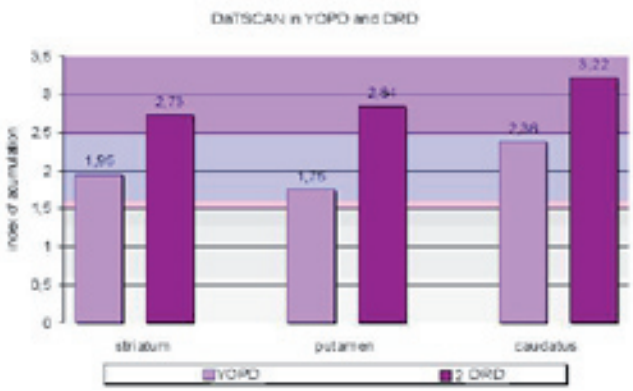

Figure 4. DaTSCAN uptake ratios in the striatum, putamen and caudatus in patients with YOPD and DRD.

Nucline SPIRIT DH-V, double-head gamma camera equipped with low-energy, parallel-hole, high-resolution collimators. Images were acquired using a full 360 rotation in step and shoot mode (128 projections, matrix 128x128, pixel size

Table 1. *Demographic, clinical characteristics and DaT SCAN findings of patients with young-onset Parkinson's disease and dopa-responsive dystonia*

Case	Age y/sex	Duration of disease/ y	Family history	Dystonia	Bradykinesia	Rigor	Tremor			Facial hypomimia	Decrease arm swing	DaTSCAN
							Regions	Rest	Postural	Action			
1	48/F	10	Yes	+RA	+RA,RL	Yes	RA,RL	Yes	Yes	No	Yes	+R	Positive
2	51/M	11	No	+N	+RA,RL	»	-	No	No	»	»	»	»
3	51/M	11	»	-	+RA,RL, +LA,LL	»	-	»	»	»	»	»	»
4	45/M	9	»	-	+RA,RL	»	-	»	»	»	»	»	»
5	33/F	1	»	-	+LA,LL	»	-	»	»	»	»	+L	»
6	32/M	1	»	+LA,LL	+LA,LL	»	LA	Yes	Yes	Yes	»	»	»
7	33/M	3 months	»	-	+RA	»	RA	»	»	»	»	+R	»
8	25/M	1	Yes	-	+RA	»	RA	»	»	»	»	»	»
9	37/F	14	»	-	+RA,RL	»	RA	»	»	No	»	+R,L	»
10	37/F	7	»	-	+RA,RL +LA,LL	No	-	No	No	»	»	+R	»
11	28/F	1	»	+RA,RL +LL	+RA,RL	Yes	RA	Yes	Yes	Yes	No	+L	Normal
12	58/F	42	No	+LL	+LA,LL	No	-	No	No	No	»	R	»
13	20/M	10	»	+LL	-	»	RA,RL LA,LL	Yes	Yes	Yes	»	-	»
Mean	38	9	5/13	6/13	12/13	10/13	7/13	7/13	7/13	5/13	10/13	12/13	10/13

RA: Right arm, RL: Right leg, LA: Left arm, LL: Left leg, R: Right, L: Left, N: Neck. M: male, F: female

3,84mm, 40sec per projection). Image reconstruction was performed using filtered back projection method, with Butterworth filter (cut off 0.5, order 7) and attenuation correction (Chang's method, factor 0.12).

The images were evaluated by visual and semiquantitative analyses of striatal binding. The ratio of specific-striatal to nonspecific-occipital binding was calculated by positioning regions of interest (ROI) on the referents transverse slice

(representing the most intense striatal uptake) on both striata (caudate nucleus, putamen) and occipital regions.

Results

Demographic and clinical findings of our patients are found in Table 1. Ten out of the 11 patients with YOPD had decreased accumulation of the tracer in striatum and especially in putamen, which are typical findings for Parkinson's disease. Seven patients (cases 1, 2 and 4-8) had bilaterally decreased tracer uptake in the striatum, particularly in putamen (Fig. 1). Three patients (cases 3, 9 and 10) had advanced disease with severe loss of nigrostriatal neurons and bilateral decreased acumulation of the tracer in striatum and increased accumulation outside striatum (Fig. 2). DaTSCAN confirmed the diagnosis of YOPD in ten patients and in three patients (cases 11-13) was normal (Fig. 3) with symmetric tracer uptake in both striata (caudate nucleus, putamen). Therefore, the diagnosis of DRD was hypothetical. Two patients with initial dystonic symptoms, and genetically proved DRD had normal findings (cases 12, 13). In one patient (case 11) initial diagnosis of YOPD after normal scan findings was changed to DRD. Semiquantitative ROI analyses of specific-striatal to nonspecific-occipital binding ratio supported our visual assesment (Fig. 4). Regions of interest (ROI) analyses have shown significantly lower ^{123}I -FP-CIT binding ratios in YOPD than in DRD in all regions of interest: striatum (1.95±0.32) vs (2.76±0.10) P<0.001, putamen (1.76±0.25) vs (2.84±0.14) P<0.0001, caudatus (2.37±0.51) vs (3.27±0.14) P<0.01. The greatest decrease was found in putamen.

Discussion

Since our results revealed significantly lower ^{123}I FP-CIT binding ratios in nigrostriatal dopaminergic system in patients with YOPD than in those with DRD this could be a useful diagnostic tool in clinical practice to differentiate parkinsonism with degenerative loss of dopaminergic nerve terminals-YOPD from parkinsonism without nigrostriatal degeneration- DRD.

Clinical findings of YOPD and DRD overleap and differential diagnosis between these conditions can be difficult. Furthermore, in both diseases family history can be present. Familial cases of DRD show an autosomal dominant mode of inheritance with incomplete penetrance and variable expression within family members, although they carry the same mutation. Some family members have clinical picture of dystonia, while others have parkinsonism and are easily misdiagnosed as YOPD [24]. On the other hand, hereditary components play a greater part in the origin of YOPD than of older-onset Parkinson's disease. About 50% of patients with YOPD and a positive family history have parkin mutation [4]. However, familial cases with typical clinical picture of DRD and parkin mutations are described [24]. Genetic analysis may help, but it is not always available and not for all patients. Furthermore, a patient has been reported with DRD mutation (GCH-I), clinical manifestations of dystonia and parkinsonism and neurodegeneration shown with DAT imaging [25]. These diseases overlap and it is difficult to distinguish them, in some cases, as also in our cases (Table 1).

Semiquantitative analysis of SPET images for our two groups of patients YOPD and DRD showed a significant difference in striatal uptake of ^{123}I-FP-CIT between these two groups. Patients with YOPD had decreased striatal uptake of dopamine transporter ligand ^{123}I-FP-CIT, while DRD group had normal ^{123}I-FP-CIT striatal uptake.

Our DaTSCAN findings were similar to other studies which reported normal findings with another DAT binding tracer ^{99m}Tc-TRODAT in patients with DRD and pathological findings in YOPD [20]. Normal dopamine transporter density measured by [^{123}I]-beta-CIT in DRD and significantly higher DAT binding in dopaminergic nerve terminals in DRD patients than in patients with YOPD was reported [16, 17].

Others described normal DaTSCAN in juvenile-onset dystonia, with DRD presentation and pathological DaTSCAN in parkinsonism [21]. There was no loss of striatal dopamine transporters and D2 receptors in patients with autosomal recessive dopa- responsive dystonia measured by FP-CIT [18]. Multi-tracer PET study with DAT tracer and receptors (D1, D2) tracers have shown that dopamine transporter binding and D1 receptors is normal in DRD, and striatal D2 receptors are increased [22].

Listed SPET and PET studies with dopamine transporter and neuroreceptors radioligands have shown that changes in striatal dopaminergic system in DRD is different from that reported in YOPD.

In conclusion, this study indicated that normal uptake of ^{123}I-FP-CIT in DRD and decreased uptake in YOPD can be a useful diagnostic tool in clinical practice in differentiating these two diseases.

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The authors declare that they have no conflicts of interest.

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