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# The symptoms asymmetry of drug-induced parkinsonism is not related to nigrostriatal cell degeneration: a SPECT-DaTSCAN study

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## ABSTRACT

**Aim.** Drug-induced parkinsonism (DIP) is the most common form of parkinsonism after Parkinson's disease (PD) itself. It has been widely believed that DIP is characterised by symmetry of symptoms. Studies of patients with DIP in whom PD had been ruled out by SPECT-DaTSCAN have shown that symptom asymmetry is a common element of DIP clinical presentation. The aim of our study was to determine whether the asymmetry of symptoms in DIP is related to any abnormality within the presynaptic part of the nigrostriatal dopaminergic system.

**Materials and methods.** Eleven patients with the diagnosis of DIP and asymmetric symptoms were studied. Their individual SPECT-DaTSCANs were normal. Indices calculated for the whole group of radiotracer uptake in the whole striatum, putamen and caudate contralateral to more severe DIP symptoms were compared to values obtained in the opposite hemisphere.

**Results.** We did not find significant differences in radiotracer uptake in structures contralateral to more severe clinical symptoms when compared to the homolateral hemisphere.

**Conclusions.** Our results have not confirmed the presence of a presynaptic nigrostriatal deficit which could be related to asymmetry of DIP. The factors responsible for the asymmetry of DIP symptoms should be sought in the postsynaptic part of the nigrostriatal dopaminergic system.

**Key words:** drug-induced parkinsonism, asymmetry of symptoms, presynaptic nigrostriatal deficit, SPECT-DaTSCAN (*Neurol Neurochir Pol 2019; 53 (4): 311–314*)

## Introduction

Idiopathic Parkinson's disease (PD) and drug-induced parkinsonism (DIP) are the two most common forms of parkinsonism [1, 2]. In PD, motor symptoms are caused by neurodegeneration of presynaptic neurons of the nigrostriatal dopaminergic system, while DIP is related to the post-synaptic dopaminergic receptor blockade within the striatum. The differential diagnosis of PD and DIP can be a challenge, especially in older people, because increasing age is a recognised as a risk for both these conditions [1, 2]. It is very important to identify persons with PD in a group of patients taking dopamine receptor blocking agents (DRBA) and in whom parkinsonism has developed because the treatment and prognosis are completely different. Therefore, attention has been paid to differences in the clinical presentations of PD and DIP, which could be useful in differential diagnosis. It has generally been assumed that DIP is characterised by symmetry of symptoms, the absence of rest tremor, and the co-occurrence of bucco-linguo-masticatory dyskinesia and akathisia [1–3].

$^{123}$I-Ioflupane (DaTSCAN®, GE Healthcare) is a dopamine transporter (DAT) radioligand for single-photon emission

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tomography (SPECT). A SPECT-DaTSCAN is used as a marker of integrity of the presynaptic part of the nigrostriatal dopaminergic system [4, 5]. Studies of patients diagnosed with DIP, in whom SPECT-DaTSCAN had excluded the coexistence of PD, have shown that the symptomatology of these two conditions shows many similarities and that asymmetry of symptoms is common in DIP [6–9]. The aim of our study was to determine whether the asymmetry of symptoms in DIP is related to any abnormality within the presynaptic part of the nigrostriatal dopaminergic system.

## Material and methods

### Patients

Our study initially enrolled 13 consecutive patients who underwent SPECT-DaTSCAN for the differential diagnosis between DIP and PD. In two of these subjects the imaging revealed abnormalities consistent with neurodegenerative parkinsonism. The remaining 11 patients (eight females and three males, mean age 64 years) were included into the study. All of them presented at least two of the three main (bradykinesia, rigidity, rest tremor) parkinsonian symptoms, and these symptoms were either asymmetric or unilateral. Subjects with signs suggesting an atypical parkinsonian syndrome, or other neurological conditions, were not included.

The duration of exposure to drugs implicated in DIP ranged from 2-14 years, while parkinsonian symptoms had lasted from 1-84 (mean 18.6) months. The onset of parkinsonism was subacute or chronic. The time from the start of psychiatric treatment to the development of parkinsonian symptoms ranged from 3-24 months. Patients were treated with different drugs and some of them received two or more drugs at the same time. The drugs most commonly used in this group at the time of the evaluation of parkinsonism were risperidone, aripiprazole, olanzapine and perazine.

### SPECT-DaTSCAN

SPECT/CT acquisitions were performed with double-head hybrid gamma-camera Infinia Hawkeye GE 4 h after i.v. administration of 5 mCi of 123I-Ioflupane. Prior to radiotracer injection, patients received orally potassium iodine to block thyroid uptake of free radioactive iodide. Data was acquired with the use of low energy high resolution (LEHR) collimators in dual energy window: 159 keV ± 10% (scatter: 130 keV ± 10%), in 128 × 128 matrix. Using a step-and-shoot method, 120 projections lasting 45 s each were registered with the use of zoom equal 1.5. Images reoriented to the orbitomeatal plane were reconstructed with the OSEM method (2 iter., 10 sub., postfilter: Butterworth 0.50/10) with scatter correction and attenuation correction (Chang method).

The analysed SPECT-DaTSCAN variables were 123I-Ioflupane uptake ratios in the entire striatum, putamen and caudate in both hemispheres. SPECT-DaTSCAN images were analysed semi-quantitatively by a nuclear medicine physician expert in neuroimaging. The quantitative assessment of DaTSCAN-SPECT images was made using DaTQUANT delivered by GE Healthcare.

In order to ascertain the relationship between the asymmetry of clinical symptoms of DIP and the result of the SPECT-DaTSCAN, the indices of radiotracer uptake in the whole striatum, putamen and caudate contralateral to more severe symptoms were compared to the respective values obtained in the opposite hemispheres. Moreover, putamen/caudate ratios for both sides were calculated.

The distribution of indices of tracer uptake obtained on both sides in each structure were compared by means of the Wilcoxon test for paired samples.

## Results

The individual SPECT-DaTSCAN results of all patients were considered to be normal. Indices of 123I-Ioflupane uptake in the whole striatum, putamen and caudate for both sides, as well as the values of the putamen/caudate ratio, are presented in Table 1.

## Discussion

DIP is the most common form of parkinsonism after PD [1, 2]. The diagnosis of DIP is relatively easy provided that there is an unequivocal temporal relationship between the DRBA introduction and the occurrence of parkinsonism, and even more so if discontinuation of offending drug leads to the resolution of DIP symptoms.

However, DIP can develop gradually after prolonged exposure to neuroleptic and, moreover, DIP can persist despite discontinuation of the drug. In such cases, it may be suspected that the patient being treated with DRBA develops PD, and the neuroleptic only contributes to its earlier manifestation. This is referred to as 'unmasking of PD by DRBA' [8, 10].

Both for the psychiatrist and for the neurologist it is crucial to decide whether the patient has pure DIP or Parkinson's disease, the course of which could have been modified by the DRBA administration. The differential diagnosis between PD and DIP can be challenging, especially because both forms of pathology can co-exist. This applies primarily to the elderly population.

In the past, this differentiation was based on clinical symptoms. It was widely believed that DIP is characterised by symmetry of symptoms, lack of tremor or the presence of postural tremor, the occurrence of bucco-lingual-masticatory dyskinesia, and akathisia [1–3].

In clinical practice, a SPECT-DaTSCAN is performed to differentiate between neurodegenerative parkinsonisms (e.g. PD) on the one hand, and on the other hand parkinsonian syndromes without presynaptic involvement (e.g. DIP) of the nigrostriatal dopaminergic system [9, 11, 12]. Studies of patients with DIP in whom the co-existence of PD has been

**Table 1.** Results of DaTSCAN imaging. Indices of radiotracer uptake (normalised to nonspecific uptake in occipital cortex) the whole striatum, putamen and caudate are presented. Moreover, putamen/caudate ratios for both sides were calculated

| Structure | Side | Indices of radiotracer uptake | | | p* |
|---|---|---|---|---|---|
| | | Mean ± SD | Minimum-maximum | Median | |
| Striatum | Contralateral | 2.54 ± 0.29 | 1.85–2.94 | 2.61 | 0.59 |
| | Ipsilateral | 2.57 ± 0.32 | 1.79–2.97 | 2.64 | |
| Putamen | Contralateral | 2.41 ± 0.31 | 1.74–2.80 | 2.47 | 0.51 |
| | Ipsilateral | 2.44 ± 0.32 | 1.64–2.82 | 2.51 | |
| Caudate | Contralateral | 2.83 ± 0.32 | 2.12–3.25 | 2.91 | 0.88 |
| | Ipsilateral | 2.86 ± 0.34 | 2.09–3.26 | 2.94 | |
| Putamen/caudate | Contralateral | 0.89 ± 0.07 | 0.81–1.02 | 0.88 | 0.72 |
| | Ipsilateral | 0.89 ± 0.03 | 0.86–0.98 | 0.88 | |

Contralateral — side opposite to the side where the symptoms of DIP were more severe; Ipsilateral — side where the symptoms of DIP were more severe; *Wilcoxon test for paired samples

ruled out by SPECT-DaTSCAN have shown that symptom asymmetry is a not uncommon element of DIP clinical presentation.

Some authors have reported asymmetry of symptoms to be less common than symmetry in DIP [6, 7], while others have not found significant differences in asymmetry of tremor, bradykinesia and stiffness between patients with a normal and an abnormal SPECT-DaTSCAN [8]. A recently published study [9] revealed asymmetry of symptoms in 88% of subjects with a diagnosis of DIP and a normal SPECT-DaTSCAN. The cause of the asymmetry of DIP symptoms has never been studied or discussed to date.

The term 'unmasked PD' has not been clarified so far. It was usually used for cases when the symptoms of parkinsonian syndrome appeared after neuroleptic administration and where the SPECT-DaTSCAN showed asymmetric deficit of the presynaptic part of the nigrostriatal system.

Prospective studies carried out in patients with REM Sleep Behaviour Disorder (RBD), which is a pre-motor manifestation of PD and other synucleinopathies, have shown that nigrostriatal dopaminergic deficit is a slowly but steadily increasing phenomenon in the early phase of the disease [13, 14]. In RBD subjects who remained parkinsonism free, 123I-Ioflupane uptake reduction was more pronounced in the putamen than it was in the caudate nucleus [13]. It can be assumed that even at an early, premotor stage of PD, when the individual SPECT-DaTSCAN result remains within the normal range, there may be a subtle asymmetry in the number of dopaminergic cells in the substantia nigra, and that this asymmetry is unmasked when the patient develops DIP. However, our results seem to exclude this possibility.

## Conclusions

Our results have not confirmed the presence of a presynaptic nigrostriatal deficit which could be related to asymmetry of DIP.

## Future directions

The factors responsible for the asymmetry of DIP symptoms should be sought in the postsynaptic part of the nigrostriatal dopaminergic system.

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