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Editor's comment: Differentiating drug-induced parkinsonism (DIP) from Parkinson's disease (PD) can be a difficult and frustrating exercise for both patient and physician. To make matters even more difficult, individuals with incipient PD may be more prone to develop DIP because of already reduced dopaminergic reserve. Thus, this very useful review by Brigo and colleagues cogently summarizes the information available regarding the usefulness of various approaches and procedures in separating these two entities. They describe the value of some nonmotor features of PD, especially olfactory dysfunction, in distinguishing between PD and DIP. They also provide very useful information on which procedures are useful (DaT-scan and MIBG scanning) and which do not seem to be (transcranial sonography of the substantia nigra) in making this differentiation.

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Review

Differentiating drug-induced parkinsonism from Parkinson's disease: An update on non-motor symptoms and investigations

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ABSTRACT

Drug-induced parkinsonism is the second most common cause of parkinsonism after Parkinson's disease and their distinction has crucial implications in terms of management and prognosis. However, differentiating between these conditions can be challenging on a clinical ground, especially in the early stages. We therefore performed a review to ascertain whether assessment of non-motor symptoms, or use of ancillary investigations, namely dopamine transporter imaging, transcranial sonography of the substantia nigra, and scintigraphy for myocardial sympathetic innervation, can be recommended to distinguish between these conditions.

Among non-motor symptoms, there is evidence that hyposmia can differentiate between patients with "pure" drug-induced parkinsonism and those with degenerative parkinsonism unmasked by an anti-dopaminergic drug. However, several issues, including smoking history and cognitive functions, can influence smell function assessment. Higher diagnostic accuracy has been demonstrated for dopamine transporter imaging. Finally, preliminary evidence exists for sympathetic cardiac scintigraphy to predict dopaminergic pathway abnormalities and to differentiate between drug-induced parkinsonism and Parkinson's disease.

Imaging of the dopaminergic pathway seems to be the only, reasonably available, technique to aid the differential diagnosis between drug-induced parkinsonism and Parkinson's disease.

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1. Introduction

Drug-induced parkinsonism (DIP) has been deemed the most prevalent form of secondary parkinsonism in the Western world and the second most common cause of parkinsonism after idiopathic Parkinson's disease (PD) [1]. DIP was initially

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described as a complication of antipsychotic agents, but later recognized as possible side effect of a number of other compounds including antiemetics, cholinomimetics, antidepressants, anti-vertigo medications, calcium channel antagonists, antiarrhythmics, and antiepileptic drugs [2]. The raising prevalence of DIP is likely due to the increasing life expectance of the population, since there is an age-related attrition of nigrostriatal dopamine neurons [3]. Moreover, as people age, they are more frequently subjected to polypharmacotherapy, particularly for behavior-related disorders, which are relatively common among the elderly.

Although being very frequent, there are no widely accepted diagnostic criteria for DIP. The latter is presumed when a parkinsonian syndrome develops during treatment with a potential offending medication (usually a dopamine receptor blocking drug) [1]. Symptoms should recover within 6 months of withdrawal of drug treatment, if applicable [4]. However, the exposure to an offending drug can not be taken alone as the final proof to make a diagnosis of DIP, since symptoms, in a number of cases, do not improve or even worsen after that the "offending" drug has been withdrawn [5], raising the suspicion of the concomitant development of PD. A number of clinical clues have been highlighted to aid the differential diagnosis between DIP and PD, and these include symmetry of symptoms, relative absence of rest tremor, coexistence of oro-mandibular dyskinesias and a less pronounced, if any, response to the levodopa [6]. However, DIP can be clinically indistinguishable from PD in a number of patients [6–9].

A few studies have been recently conducted to assess whether certain non-motor symptoms (NMS) or ancillary investigations, including dopamine transporter imaging, transcranial sonography of the substantia nigra, and 123I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy, can help the differential diagnosis between these two conditions. Proper distinction between DIP and PD has obviously crucial consequences, with regard of both management and long-term prognosis of these patients. We therefore aimed here to review such studies in order to ascertain whether there is enough evidence for any of these techniques or for the assessment of NMS to be recommended in clinical practice to aid the differential diagnosis between DIP and PD.

2. Methods

The electronic database MEDLINE (accessed by Pubmed; 10th January 2004–10th January 2014) was searched using the free term "drug-induced parkinsonism" to find relevant articles. No language restrictions were applied. All the titles and abstracts of publications identified by the search were evaluated for their eligibility. We excluded studies conducted in animals, case reports, letters, editorials, and narrative reviews. Studies reporting data on non-motor symptoms (NMS) or ancillary investigations potentially helpful in the differential diagnosis between these PD and DIP were considered eligible and, therefore, those focusing only on motor symptoms of DIP have been excluded. We excluded publications that did not meet preliminary criteria at this stage. Following screening, we assessed the full-text of potentially eligible citations for inclusion.

3. Results

3.1. Non-motor symptoms

Patients with PD commonly manifest NMS since the earliest stage of disease [10] and some NMS such as hyposmia and sleep disturbances can also predate the motor onset in PD [11]. NMS likely reflect involvement of both dopaminergic and non-dopaminergic systems in PD [12] and this, theoretically, is not to be expected in DIP.

Kim and colleagues have recently evaluated presence of NMS in 28 patients with DIP, 35 drug-naïve patients with PD, and 32 healthy controls, using the Non Motor Symptoms Scale (NMSS). They found that the NMSS total score was higher in PD patients than in subjects with DIP and healthy controls. Moreover, after having controlled for age and gender, such NMS as urinary and sleep disturbances, attention deficit, and hyposmia were found to be significantly associated with PD [13]. The notion that hyposmia can accurately discriminate between PD and DIP patients, has been further confirmed by others [14–16]. Using the Sniffin' Sticks test (SST) in 16 DIP patients, 13 PD patients and 19 healthy controls, Bovi et al. found that DIP patients (with normal dopaminergic imaging as assessed by means of [(123)I] FP-CIT SPECT – DaT-Scan) had smell function similar to healthy controls. On the other hand, a subgroup of patients with DIP had impaired smell function and this predicted an abnormal dopaminergic imaging, suggesting that these patients had eventually developed degenerative PD [15]. Similar results were found by Morley et al.: hyposmia was significantly more common among subjects with PD than in those with DIP, and olfactory testing correctly predicted whether subjects would have recovered after drug withdrawal in 11/13 cases (unpublished data) [16]. Lee and colleagues further provided support to the value of smell function assessment in the differential diagnosis between DIP and PD (the results of this study are detailed below, see cardiac MIBG scintigraphy section) [14]. Conversely, Kruger and colleagues have reported that among 59 depressed patients treated with antipsychotic drugs, 15 developed DIP and had worse smell function (assessed by mean of SST) than patients who did not develop DIP [17]. However, there are a few aspects including absence of control groups of PD patients and/or healthy subjects, the cross-sectional study design with no follow-up, and lack of imaging techniques to exclude pre-clinical PD unmasked by the offending drug, which greatly limit the results of this study.

Other studies have focused on cognition in DIP. When compared to schizophrenic patients without DIP, those with DIP complain more frequently about cognitive disturbances [18]. Severity of DIP has been also found to correlate with the severity of subjective cognitive complaints [19], suggesting that cognitive issues can be directly linked to the DIP rather than to the treatment or to the associated psychiatric condition. A subsequent study tried therefore to address the characteristics of the cognitive impairment associated with DIP [20]. An extensive neuropsychological battery assessing memory, attention/executive, visuospatial, and language functions, was administered to 91 patients with PD, 13 patients with DIP and 22 healthy controls. Although cognitive function in DIP patients was significantly worse than in control in several domains, no significant differences were found with PD patients, apart from the copy of the Rey complex figure and the contrasting program. No other tests were performed to assess whether visuospatial functions can accurately discriminate between DIP and PD patients, whereas other tests assessing frontal functions failed to confirm the trend observed with the contrasting program. These findings suggest that cognitive impairment is common among DIP patients, but that there is no clear cognitive pattern, which can aid the differential diagnosis between DIP and PD.

A summary of the aforementioned studies is provided in Table 1. Overall, a few evidence supports smell function assessment to aid the differential diagnosis between DIP and PD. Moreover, there are preliminary suggestions highlighting that such NMS as urinary and sleep symptoms are suggestive of PD rather of DIP, but further studies with objective measurements of urinary and sleep impairment are warranted to clarify their role in the differential diagnosis.

3.2. Transcranial sonography of the substantia nigra

Transcranial sonography (TS) of the substantia nigra has been recently proposed as a useful technique in the diagnosis of

Table 1
Clinical studies assessing non-motor symptoms.

Study	Type of NMS assessed	Population	Method	Main findings
Kim et al., 2013	Several NMS	35 drug-naïve PD in the early stages, 28 DIP, 32 healthy controls	Non motor symptoms scale (NMSS)	The total NMSS score was higher in PD than in DIP patients. Urinary symptoms, sleep disturbances, attention deficit, and hyposmia were significantly associated with PD.
Lee et al., 2007	Olfactory impairment	24 PD, 15 DIP, 15 healthy controls	Cross cultural smell identification (CSSI) test and cardiac 123I-MIBG scintigraphy	Smell function was impaired in PD patients but not in those with DIP. No difference between DIP patients and healthy controls.
Bovi et al., 2010	Olfactory impairment	13 PD, 16 DIP, 19 healthy controls	"Sniffin'Sticks" test and [(123)I] FP-CIT SPECT	Patients with DIP and pathological putamen uptake had abnormal olfactory function. DIP patients with normal putamen uptake showed smell functions similar to control subjects.
Morley et al., 2013	Olfactory impairment	13 DIP	Not explicitly reported	Hyposmia was significantly more common among PD patients compared with DIP, and olfactory testing correctly predicted whether subjects would recover after drug withdrawal in 11/13 cases (unpublished data).
Kruger et al., 2008	Olfactory impairment	59 depressed patients treated with antipsychotic drugs (15 patients with DIP)	"Sniffin' Sticks" test	Olfaction was found to be worse in DIP patients when compared to those who did not develop DIP
Kim et al., 2008	Cognition	58 Schizophrenic patients with (34)/without (24) DIP	Frankfurt complaint questionnaire	Patients with DIP had more cognitive complaints
Kim et al., 2009	Cognition	91 Patients with schizophrenia (61 with/30 without DIP)	Frankfurt complaint questionnaire	Severity of DIP significantly correlated with the total score of the questionnaire.
Kim et al., 2011	Cognition	91 PD, 13 DIP, 22 healthy controls	Neuropsychological tests assessing memory, attention/executive, visuo-spatial, and language functions	No significant differences between DIP and PD patients.

DIP: drug-induced parkinsonism; NMS: non-motor symptoms; PD: idiopathic Parkinson's disease; SPECT: single photon emission computed tomography.

parkinsonian syndromes [21]. In PD, an enlarged area of echogenicity in the substantia nigra, which is thought to be associated with increased iron concentrations, is observed in more of 90% of patients and might allow an early differential diagnosis [21].

In one prospective study, diagnostic accuracy of substantia nigra TS was assessed in 196 patients with clinically undetermined parkinsonism of recent onset [22]. A clinical re-evaluation after 2 years served as a surrogate gold standard and 7 subjects (3.6%) were eventually diagnosed with DIP. Hyperechogenicity of the substantia nigra had overall low sensitivity and specificity values for the diagnosis of PD (40%, CI: 30–50%; and 61%, CI: 52–70%, respectively) and therefore for its differentiation from secondary parkinsonisms such as DIP.

A further prospective study used substantia nigra TS to specifically evaluate 20 patients with suspected DIP [23]. These patients were clinically re-assessed after a minimum time of 6 months after discontinuation of the anti-dopaminergic drug and classified as affected by DIP if parkinsonism had resolved or, alternatively, as subclinical drug-exacerbated parkinsonism if symptoms persisted/worsened thereafter. No statistically significant differences as to the hyperechogenicity in the substantia nigra or in the lentiform nucleus were found between the two groups. Combined assessment of TS alterations in both structures had a negative predictive value of 85.7% for diagnosis of DIP, with a negative likelihood ratio of 0.3.

Details of such studied are provided in Table 2. Overall, there is not yet enough evidence to support the use of TS of the substantia nigra for the differential diagnosis between DIP and PD.

3.3. Dopamine transporter imaging

SPECT using (123) I-ioflupane (FP-CIT) as dopamine transporter ligand (DaT-Scan) is the only approved technique to differentiate PD form other tremulous disorders [24]. The formal indications for the DaT-scan, however, do not cover the differential diagnosis between PD and symptomatic parkinsonisms (including DIP) [24] and therefore its role in such cases remains controversial.

A body of evidence has been produced suggesting that the DaT-Scan can be a reliable technique to differentiate between PD and DIP patients with relatively good sensitivity and specificity values [25–27]. On the other hand, several studies have also shown that a number of DIP patients can show an abnormal DaT-Scan. Such subgroup has been deemed to reflect sub-clinical PD unmasked by the anti-dopaminergic drugs rather than true DIP and, in fact, in these patients motor symptoms do not recover after that the offending drug has been withdrawn [28–34]. Moreover, this sub-group is more likely to benefit from levodopa therapy [32,34], further supporting the notion that these patients have PD unmasked by anti-dopaminergic drugs rather than true DIP due to blockade of post-synaptic dopaminergic receptors. A further prospective study has confirmed that, after adjustment for possible confounders, abnormal DaT-Scan findings at baseline were the only predictor of subsequent motor disability progression and better outcome following levodopa treatment [34].

In summary, there is enough evidence to deem the DaT-Scan as a useful technique for the differential diagnosis between DIP and PD (Table 2). Patients treated with anti-dopaminergic drugs who develop parkinsonism can be in fact classified into two broad groups: 1) those in whom parkinsonian symptoms are only due to blockade of post-synaptic dopamine-receptors by an offending agent, (these patients have normal SPECT findings and no evidence of disease progression at follow-up); and 2) those in whom a subclinical nigro-striatal degeneration is unmasked by anti-dopaminergic treatment and symptoms progress after the offending drug has been withdrawn. SPECT findings might also predict

Table 2
Clinical studies assessing transcranial sonography of the substantia nigra, dopamine transporter imaging, and scintigraphy for myocardial sympathetic innervation.

Study	Objective	Population	Method	Main findings
Bouwmans et al., 203	Investigate the diagnostic accuracy of substantia nigra TS in	196 Patients with clinically undetermined parkinsonism of recent onset (7 patients eventually diagnosed with DIP)	Substantia nigra TS	Low sensitivity (40%, CI 30–50%) and specificity (61%, CI 52–70%) for PD Substantia nigra TS is not enough accurate to differentiate PD from other parkinsonian syndromes such as DIP
Olivares Romero et al., 2013	Investigate substantia nigra TS findings in DIP patients	20 PD, 20 possible DIP (15 eventually diagnosed with definite DIP, 5 eventually diagnosed with subclinical drug-exacerbated parkinsonism)	Substantia nigra and lentiform nucleus TS	Combined assessment of TS alterations in both substantia nigra and lentiform nucleus had a negative predictive value of 85.7% for diagnosis of definite DIP, with a negative likelihood ratio of 0.3
Vlaar et al., 2008	Investigate the diagnostic accuracy of I-123-FP-CIT SPECT in differentiating between PD and DIP	248 patients with parkinsonism	I-123-FP-CIT SPECT	Mean odds ratio to distinguish between PD and DIP of 36 (95% CI 2–296)
Diaz-Corrales et al., 2010	Investigate the diagnostic accuracy of I-123-FP-CIT SPECT in differentiating between PD with/without antidopaminergic treatment and DIP	25 PD unmasked by antidopaminergic drugs, 22 PD without a previous antidopaminergic treatment, 32 DIP	I-123-FP-CIT SPECT	Normal results in 29 (90.6%) patients with DIP and abnormal in all patients with PD (qualitative assessments of SPECT images).
Cuberas-Borros et al., 2011	Investigate the diagnostic accuracy of I-123-FP-CIT SPECT in differentiating between PD, DIP, and essential tremor	20 PD, 20 DIP, 20, essential tremor	I-123-FP-CIT SPECT	Uptake decrease in the putamen nuclei was found only in PD
Olivares Romero et al., 2013	Investigate the diagnostic accuracy of I-123-FP-CIT SPECT in differentiating between iatrogenic parkinsonism and subclinical drug-exacerbated parkinsonism	19 DIP evaluated at least 6 months after discontinuation of antidopaminergic drugs	I-123-FP-CIT SPECT	Sensitivity of 66.7%, specificity and positive predictive value of 100%, negative predictive value of 86.7%, and a negative likelihood ratio of 0.33 for diagnosis of iatrogenic parkinsonism or subclinical drug-exacerbated parkinsonism.
Tinazzi et al., 2008	To investigate the status of dopamine nerve terminals in DIP patients following antidopaminergic therapy	32 DIP, 26 healthy controls	I-123-FP-CIT SPECT	SPECT binding was reduced in 14 patients (PD unmasked by the anti-dopaminergic medication) and normal in 18 patients. Symmetry of parkinsonism and bucco-linguo-masticatory dyskinesias more frequent in patients with normal tracer binding.
Tinazzi et al., 2009	To investigate the status of dopamine nerve terminals in DIP patients following antidopaminergic therapy	10 DIP with normal I-123-FP-CIT SPECT binding (group 1), 9 DIP with abnormal I-123-FP-CIT SPECT binding (group 2).	I-123-FP-CIT SPECT performed at 19–39-month follow-up	At follow-up, SPECT was still normal and UPDRS motor score values did not progress in all patients of the group 1. Conversely, both putaminal dopaminergic denervation on the scan and UPDRS motor scores progressed at follow up in group 2. Levodopa treatment improved motor symptoms in 30% of the patients in group 1 and in 88.9% of patients in group 2.
Tinazzi et al., 2012	To estimate the prevalence of DIP and, among patients with DIP, the prevalence of I-123-FP-CIT SPECT abnormalities in schizophrenic patients.	448 Schizophrenic patients treated with antipsychotics for at least 6 months	I-123-FP-CIT SPECT	DIP was identified in 149 out of 448 patients (33%). Neuroimaging abnormalities were found in 41 of 97 DIP patients who underwent SPECT (42%). The latter group was deemed to have PD unmasked by the offending drug.
Tinazzi et al., 2013	To investigate the status of dopamine nerve terminals in DIP patients	60 patients with schizophrenia and parkinsonism with I-123-FP-CIT SPECT at baseline evaluation (normal SPECT = 33; abnormal SPECT = 27)	I-123-FP-CIT SPECT performed at 2-years follow-up	Patients with baseline abnormal SPECT had higher UPDRS motor scores at follow-up and were more likely to respond to levodopa treatment.

(*continued on next page*)

Table 2 (*continued*)

Study	Objective	Population	Method	Main findings
				Abnormal SPECT findings at baseline were the only predictor of motor disability progression and of better outcome following levodopa treatment
Lee et al., 2006	Investigate the role of 123I-MIBG scintigraphy in differentiating between DIP and PD	20 patients with DIP, 32 with PD, 20 healthy controls	123I-MIBG Scintigraphy	The mean heart to mediastinum ratio was significantly greater in patients with DIP than in those with PD; MIBG uptake was not different between the DIP patients and controls; two DIP patients whose MIBG uptake was reduced showed persistent parkinsonism with a dramatic response to levodopa
Lee et al., 2007	Investigate olfactory function and its relation to cardiac 123I-MIBG uptake in patients with DIP	15 patients with DIP, 24 patients with PD and 15 healthy controls	Mean cross cultural smell identification odour test (CCSI) score; 123I-MIBG scintigraphy	Smell function was found to be normal in 93% of patients with DIP, and all DIP patients with a normal CCSI score had also normal cardiac MIBG uptake. One DIP patient whose CCSI score was significantly reduced also had decreased cardiac MIBG uptake
Kim et al., 2012	Diagnostic accuracy of combined use of 123I-MIBG scintigraphy and FP-CIT PET in distinguishing the prognosis in DIP patients	20 patients with DIP followed for more than 2 years after withdrawal of offending drug	FP-CIT SPET and 123I-MIBG scintigraphy; clinical valutation of parkinsonism at the beginning of the study and 3,6,12,18 and 24 months after withdrawal of the offending drug	DAT uptake and MIBG uptake were found to be normal in 16 of 20 patients with DIP, and all these patients had a clinical remission of parkinsonian motor symptoms within 3 months after withdrawal of offending drug; two patients with a decrease in DAT and MIBG uptake showed persistent motor symptoms after withdrawal of offending drug; other 2 patients with a normal DAT uptake and decreased MIBG uptake showed remission of motor symptoms after withdrawal of the offending drug within 2 months, with reappearance of parkinsonian syndrome during the follow-up period.

DIP: drug-induced parkinsonism; PD: idiopathic Parkinson's disease; SPECT: single photon emission computed tomography; TS: transcranial sonography.

levodopa response and therefore provide crucial information as to the prognosis of these patients.

3.4. Cardiac 123I-MIBG scintigraphy

Several studies have shown that cardiac MIBG uptake is significantly reduced in patients with PD [35] compared to healthy controls; furthermore, it has been claimed that this technique might help differentiating PD from other forms of degenerative parkinsonism [36]. Conversely, only a few studies have assessed the role of cardiac MIBG scintigraphy in the differential diagnosis between PD and DIP (Table 2).

Lee et al. studied 20 patients with DIP cardiac MIBG scintigraphy. In up to 90% of these patients, MIBG uptake was found to be normal. The remaining two patients, who disclosed an abnormal MIBG uptake, manifested persistent parkinsonism after the withdrawal of the offending drug, and a dramatic response to levodopa treatment. This scenario bears resemblance to what has been discussed above for the DaT-Scan and highlights the fact that a number of patients can have sub-clinical PD unmasked by anti-dopaminergic treatments [37]. The same research group has also evaluated the relationship between smell function and cardiac 123I-MIBG scintigraphy in 15 DIP patients, 24 PD patients, and 15 healthy controls [37]. Smell function was found to be normal in all DIP patients with normal MIBG cardiac uptake, whereas one patient (1/15, 6.7%) with an impaired smell function had also decreased cardiac MIBG uptake and persistence of motor symptoms after withdrawal of the offending drugs, suggesting that such patient had eventually developed degenerative PD.

Interestingly, a prospective 2-year follow-up study using both [18F] FP-CIT PET and cardiac MIBG scintigraphy in DIP patients has suggested the latter to early predict subsequent development of degenerative parkinsonism [13]. Out of 20 patients, 16 showed normal DAT binding and normal myocardial sympathetic innervation and their parkinsonism resolved within 3 months after the withdrawal of the offending drug. Two patients showed instead both decreased dopamine transporter binding and impaired cardiac sympathetic innervation, and clinically worsened at follow-up, thus being deemed to have PD unmasked by anti-dopaminergic drugs. The remaining two patients had normal or very marginal reduction of DAT binding and clearly decreased MIBG uptake. These two patients fully recovered within 2 months after the drug discontinuation, but eventually developed PD within the following 2 years. A second scan showed clear decreased dopamine transporter binding, suggesting a possible role of sympathetic cardiac denervation as a very early marker of PD, as previously suggested [38].

All these studies suggest that MIBG cardiac scintigraphy might be a promising technique to aid the differential diagnosis between DIP and PD. Further studies with larger samples are needed in this regard.

4. Conclusions

Clinical differentiation between DIP and PD can be challenging in the early stage of the disease. Proper distinction between DIP and PD patients has crucial implications in terms of management and prognosis. This is mainly based on the assumption that DIP is a non-degenerative condition, which should resolve after discontinuation of the causative agent, if applicable. However, a body of evidence has been produced that a number of patients have actually sub-clinical neurodegenerative parkinsonism unmasked by the offending drug. In such cases, distinction of these patients is even more challenging based on the clinical assessment of motor features.

There is preliminary evidence that some NMS such urinary and sleep disturbances, might point towards a PD diagnosis, but studies addressing this topic had a number of limitations including small samples size and cross-sectional design. More robust evidence exists for hyposmia, which seems to accurately differentiate between patients with “pure” DIP and those with degenerative PD unmasked by an offending drug. Smell function assessment is a easy, cheap and quick tool that can be routinely used in clinical practice. However, it should be also noted that smoking history, concomitant otorhinolaryngoiatric diseases, attention and cognitive status influence smell function assessment.

Higher diagnostic accuracy can be obtained by mean of dopamine transporter imaging which has been shown to reliably differentiate between patients with pure DIP and patients who have a subclinical PD unmasked by an anti-dopaminergic drug. Abnormal dopamine transporter imaging seems also to predict a good response to levodopa therapy in the latter group. Interestingly, it has been reported that an abnormal MIBG cardiac scintigraphy might predate dopamine transporter imaging abnormalities and accurately differentiate between DIP and PD patients, but further prospective long-term follow-up studies are needed to confirm this suggestion. No enough evidence exists for the TS of the substantia nigra in the differential diagnosis between DIP and PD.

Overall, dopamine transporter imaging seems to be the only, reasonably available, technique to aid the differential diagnosis between DIP and PD, although there is no specific mention in this regard in the current formal indications for the dopamine transporter imaging. Further studies are warranted to see whether some of the techniques reviewed here can be advised in the clinical practice when facing a patient supposed to be affected with DIP.

Conflict of interest

None of the authors has any conflict of interest to disclose.

References

[1] López-Sendón J, Mena MA, de Yébenes JG. Drug-induced parkinsonism. Expert Opin Drug Saf 2013;12:487–96.
[2] Mena MA, de Yébenes JG. Drug-induced parkinsonism. Expert Opin Drug Saf 2006;5:759–71.
[3] de la Fuente-Fernández R, Schulzer M, Kuramoto L, Cragg J, Ramachandiran N, Au WL, et al. Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. Ann Neurol 2011;69:803–10.
[4] Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. Neurology 1999;52:1214–20.
[5] Martí-Massó JF, Poza JJ. Cinnarizine-induced parkinsonism: ten years later. Mov Disord 1998;13:453–6.
[6] Lòpez-Sendon JL, Mena MA, de Yèbenes JG. Drug-induced parkinsonism in the elderly: incidence, management and prevention. Drugs Aging 2012;29:105–18.
[7] Hassin-Baer S, Sirota P, Korczyn AD, Treves TA, Epstein B, Shabtai H, et al. Clinical characteristics of neuroleptic-induced parkinsonism. J Neural Transm 2001;108:1299–308.
[8] Tolosa E, Coelho M, Gallardo M. DAT-imaging in drug-induced and psychogenic parkinsonism. Mov Disord 2003;18(Suppl. 7):S28–33.
[9] Lorberboym M, Treves TA, Melamed E, Lampl Y, Hellmann M, Djaldetti R. [123I]-FP/CIT SPECT imaging for distinguishing drug-induced parkinsonism from Parkinson's disease. Mov Disord 2006;21:510–4.
[10] Erro R, Picillo M, Vitale C, Amboni M, Moccia M, Longo K, et al. Non-motor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. J Neurol Neurosurg Psychiatry 2013;84:14–7.
[11] Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord 2012;27:617–26.
[12] Barone P. Neurotransmission in Parkinson's Disease: beyond dopamine. Eur J Neurol 2010;17:364–76.
[13] Kim JS, Oh YS, Kim YI, Yang D, Chung YA, IeR You, et al. Combined use of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy and dopamine transporter (DAT) positron emission tomography (PET) predicts prognosis in drug-induced Parkinsonism (DIP): a 2-year follow-up study. Arch Gerontol Geriatr 2013;56:124–8.

[14] Lee PH, Yeo SH, Yong SW, Yun JK. Odour identification test and its relation to cardiac 123I-metaiodobenzylguanidine in patients with drug induced parkinsonism. J Neurol Neurosurg Psychiatry 2007;78:1250–2.
[15] Bovi T, Antonini A, Ottaviani S, Antonioli A, Cecchini MP, Di Francesco V, et al. The status of olfactory function and the striatal dopaminergic system in drug-induced parkinsonism. J Neurol 2010;257:1882–9.
[16] Morley JF, Duda JE. Use of hyposmia and other non-motor symptoms to distinguish between drug-induced parkinsonism and Parkinson's disease. J Parkinson's Dis 2014;1:169–73.
[17] Kruger S, Haehner A, Thiem C, Hummel T. Neuroleptic-induced parkinsonism is associated with olfactory dysfunction. J Neurol 2008;255:1574–9.
[18] Kim JH, Kim SY, Byun HJ. Subjective cognitive dysfunction associated with drug-induced parkinsonism in schizophrenia. Park Relat Disord 2008;14:239–42.
[19] Kim JH, Byun HJ. Non-motor cognitive-perceptual dysfunction associated with drug-induced parkinsonism. Hum Psychopharmacol 2009;24:129–33.
[20] Kim YD, Kim JS, Chung SW, Song IU, Yang DW, Hong YJ, et al. Cognitive dysfunction in drug induced parkinsonism (DIP). Arch Gerontol Geriatr 2011;53:e222–6.
[21] Gaenslen A, Unmuth B, Godau J, Liepelt I, Di Santo A, Schweitzer KJ, et al. The specificity and sensitivity of transcranial ultrasound in the differential diagnosis of Parkinson's disease: a prospective blinded study. Lancet Neurol 2008;7:417–24.
[22] Bouwmans AE, Vlaar AM, Mess WH, Kessels A, Weber WE. Specificity and sensitivity of transcranial sonography of the substantia nigra in the diagnosis of Parkinson's disease: prospective cohort study in 196 patients. BMJ Open 2013;3. pii: e002613.
[23] Olivares Romero J, Arjona Padillo A, Barrero Hernández FJ, Martín González M, Gil Extremera B. Utility of transcranial sonography in the diagnosis of drug-induced parkinsonism: a prospective study. Eur J Neurol 2013 Mar 16. http://dx.doi.org/10.1111/ene.12131.
[24] Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry 2010;81:5–12.
[25] Vlaar AM, de Nijs T, Kessels AG, Vreeling FW, Winogrodzka A, Mess WH, et al. Diagnostic value of 123I-ioflupane and 123I-iodobenzamide SPECT scans in 248 patients with parkinsonian syndromes. Eur Neurol 2008;59:258–66.
[26] Cuberas-Borrós G, Lorenzo-Bosquet C, Aguadé-Bruix S, Hernández-Vara J, Pifarré-Montaner P, Miquel F, et al. Quantitative evaluation of striatal I-123-FP-CIT uptake in essential tremor and parkinsonism. Clin Nucl Med 2011;36:991–6.
[27] Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2013;84:1288–95.
[28] Diaz-Corrales FJ, Sanz-Viedma S, Garcia-Solis D, Escobar-Delgado T, Mir P. Clinical features and 123I-FP-CIT SPECT imaging in drug-induced parkinsonism and Parkinson's disease. Eur J Nucl Med Mol Imaging 2010;37:556–64.
[29] Lorberboym M, Treves TA, Melamed E, Lampl Y, Hellmann M, Djaldetti R. [123I]-FP/CIT SPECT imaging for distinguishing drug-induced parkinsonism from Parkinson's disease. Mov Disord 2006;21:510–4.
[30] Olivares Romero J, Ariona Padillo A. Diagnostic accuracy of 123 I-FP-CIT SPECT in diagnosing drug-induced parkinsonism: a prospective study. Neurologia 2013;28:276–82.
[31] Tinazzi M, Ottaviani S, Isaias IU, Pasquin I, Steinmayr M, Vampini C, et al. [123I]FP-CIT SPET imaging in drug-induced Parkinsonism. Mov Disord 2008;23:1825–9.
[32] Tinazzi M, Antonini A, Bovi T, Pasquin I, Steinmayr M, Moretto G, et al. Clinical and [123I]FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism. J Neurol 2009;256:910–5.
[33] Tinazzi M, Cipriani A, Matinella A, Cannas A, Solla P, Nicoletti A, et al. [^{123}I]FP-CIT single photon emission computed tomography findings in drug-induced Parkinsonism. Schizophr Res 2012;139:40–5.
[34] Tinazzi M, Morgante F, Matinella A, Bovi T, Cannas A, Solla P, et al. Imaging of the dopamine transporter predicts pattern of disease progression and response to levodopa in patients with schizophrenia and parkinsonism: a 2-year follow-up multicenter study. Schizophr Res 2014;152:344–9.
[35] Goldstein DS. Dysautonomia in Parkinson's disease: neurocardiological abnormalities. Lancet Neurol 2003;2:669–76.
[36] Rascol O, Schelosky L. 123I-metaiodobenzylguanidine scintigraphy in Parkinson's disease and related disorders. Mov Disord 2009;24(Suppl. 2):S732–41.
[37] Lee PH, Kim JS, Shin DH, Yoon SN, Huh K. Cardiac 123I-MIBG scintigraphy in patients with drug induced parkinsonism. J Neuro Neurosurg Psychiatry 2006;77:372–4.
[38] Goldstein DS, Sharabi Y, Karp BI, Bentho O, Saleem A, Pacak K, et al. Cardiac sympathetic denervation preceding motor signs in Parkinson disease. Clin Aut Res 2007;17:118–21.