123I-iomdone SPET and 123I-MIBG in the diagnosis of Parkinson's disease and parkinsonian disorders and in the differential diagnosis between Alzheimer's and Lewy's bodies dementias

Abstract

Nuclear medicine procedures are widely used as "in vivo" biomarkers in a large number of brain diseases, especially in the diagnosis of Parkinson's disease (PD) and of parkinsonian disorders (pD). Furthermore, nuclear medicine is used in the differential diagnosis of dementias especially Alzheimer's disease (AD) and dementia with Lewy's bodies (LBD) which share many clinical symptoms and often LBD is misdiagnosed as AD. The differential diagnosis between these clinical entities is crucial for treatment since LBD also shares some clinical symptoms with parkinsonian disorders. We reviewed the most relevant papers that study the usefulness of both iodine-123-iomdone studied by single photon emission tomography (123I-iomdone SPET) and of 123I-metaiodobenzylguanidine (123I-MIBG) cardiac scintigraphy in the diagnosis of PD and pD and in the differential diagnosis between AD and LBD in order to contribute to the clinical practice of the diseases.

Introduction

The term “parkinsonian disorders” or “parkinsonism” includes a large number of heterogeneous clinical entities characterized by one or more symptoms like tremor, bradykinesia, difficulty in walking and balancing, rigidity, stiffness, and cognitive impairment. Idiopathic Parkinson’s disease (PD) represents the most common parkinsonian disorder although three main categories could be considered (Table 1). Beyond the familial neurodegenerative diseases associated with parkinsonism, it is crucial, from a clinical point of view, to differentiate PD from the secondary forms of pD and distinguish PD from other atypical forms in order to plan the most appropriate therapeutic management.

All neurodegenerative diseases have a common pathogenetic molecular mechanism characterized by the abnormal accumulation of different, not degraded, normal proteins in specific neuronal population and in glial cells [1]. These data lead to the definition of proteinopathies [2] whose pathology is determined by the type of proteins and by the anatomical localization of protein deposits; therefore, two different groups can be considered, as illustrated in Table 2 [1].

Tauopathies are characterized by intracellular inclusion of hyperphosphorylated and aggregated tau proteins in the form of neurofibrillary tangles. They clinically include AD, fronto-temporal dementia with parkinsonism linked to tau mutation on chromosome 17 (FTDP-17 T), Pick disease, progressive supranuclear palsy (PSP), and cortico basal degeneration (CBD).

Alpha-synucleinopathies clinically include both PD and PD with dementia (PDD), LBD and multiple system atrophy (MSA). They are pathologically characterized by the presence of LB, consisting of aggregates of phosphorylated alpha-synuclein protein. However, from the clinical point of view, some authors observed that, despite the histopathological classification of the neurodegenerative diseases which is based on the nature and localization of these deposits in the nervous system, these pathologies could not be considered as isolated categories because the patients have doubtful or mixed clinical symptoms, especially at the early stages. These observations supported the idea that an overlap between alpha-synucleinopathies and tauopathies could be possible [2].
As a consequence, both types of intracellular inclusions, consist of the abnormal proteins tau and alpha-synuclein, are sufficient to cause neurodegeneration, but their interaction plays a more important role in the development and spread of neuropathologies [2]. Therefore, the clinical differential diagnosis of PD is often an unsolved problem, especially at the early stages, with resulting difficulties in the therapeutic management of these patients [3-5].

Among parkinsonian syndromes (pS), cognitive decline is crucial to identify patients with worse prognosis and not responding to treatments.

The most frequent misdiagnosis of PD in 25% of cases includes essential tremor (ET), vascular parkinsonism (VP), drug induced parkinsonism (DP) and pS such as MSA, PSP, CBD and LBD (3-5), all characterized by a progressive cognitive impairment. On the other hand, about 30% of MSA and PSP and more than 70% of CBD patients are not correctly diagnosed even in advanced stages [6].

Nuclear medicine procedures such as positron emission tomography (PET) and single photon emission tomography (SPET) techniques, are widely used as “in vivo” biomarker in a large number of brain diseases [7]; these two methods evaluating “in vivo” the neurotransmission assessment, the metabolic activity and the presence of abnormal proteins, represent useful tools to better understand disease pathophysiology and to diagnose the diseases in the early stage, as well as and to differentiate the various parkinsonian clinical entities, especially when these are associated with dementia.

In clinic practice, the most diffuse nuclear medicine procedures for identifying PD are focused on the study of the integrity of neurotransmitter system, in particular of the nigrostriatal dopaminergic system using I-123 ioflupane brain SPET and the postganglionic presynaptic cardiac sympathetic innervation using I-123-metaiodobenzilguanidine (MIBG) cardiac scintigraphy.

Alzheimer’s disease (AD) and dementia with Lewy bodies (LBD) share many clinical symptoms and often LBD is misdiagnosed as AD; so, the differential diagnosis between these clinical entities is important.

We reviewed the most relevant papers that investigated the usefulness of both I-123 ioflupane brain SPET and I-123-MIBG cardiac scintigraphy in the diagnosis of PD and PD associated with cognitive impairment and dementia and also we reviewed the differential diagnosis of AD and LBD in order to contribute in clarifying which role these two procedures may play in clinical practice.

### Diagnosis of Parkinson’s disease and parkinsonian syndromes

#### Dopaminergic system evaluation
The most useful brain SPET procedures are based on the evaluation of nigrostriatal system function since the pathophysiologic origin of numerous symptoms of PD and of other neurodegenerative disorders are represented by the degeneration of dopaminergic neurons in the pars compacta of the substantia nigra and the consequent progressive reduction in dopamine production [8, 9].

The synthesis of the neurotransmitter dopamine starts from tyrosine through the intermediate steps of hydroxylation and decarboxylation. The synthesis is regulated by many factors, including the inhibition of tyrosine hydroxylase, the release of dopamine in the synaptic space and the density of the postsynaptic dopaminergic receptors. This self-regulating system is able to compensate for a long time neuronal loss, thus delaying the onset of clinical symptoms, which occur only when the neuronal dopaminergic damage becomes severe and accounts for 60%-70% [8, 10].

From a clinical point of view, SPET radiotracers that provide useful information about the functional integrity of dopaminergic system in an extremely early phase, could be subdivided in two different groups, based on the interaction of the receptors: a) The presynaptic dopamine transporters (DaT), that represent the membrane protein regulating the dopamine reuptake from the synaptic space and can be evaluated by selective cocaine derived radiotracers and b) The striatal dopamine D2 receptors which can be studied by a benzamide derived gamma-emitting compound [11] (Table 3).

123I-ioflupane brain SPET

Among the DaT radiotracers, 123I-ioflupane is the most diffuse and widely used in clinical practice [12] and also in the differential diagnosis of dementias. The use of this cocaine analogue which is used as a SPET radiopharmaceutical in evaluating nigrostriatal presynaptic system has been approved in Europe and the United States for decades. The high affinity for DaT, its high specificity attributable to the high ratio between the rapid equilibrium in 3-6h after the intravenous (i.v.) injection [13] as well as the absence of serious adverse reactions [14] make this radiotracer the ideal tool in evaluating dopaminergic system (Figure 1).

The effectiveness of 123I-ioflupane SPET scan in improving the correct clinical diagnosis of PD was evaluated in a large number of different multicentric studies as follows:

In a multicenter study patients were enrolled from six different centers. One hundred fifty eight patients were considered as affected by parkinsonism, 27 were classified as ET and 35 were healthy volunteers. Images by 123I-ioflupane SPET were evaluated by the “institutional on-site readers” and also by a group of five expert nuclear medicine physicians blinded to patients’ clinical data [15]. Sensitivity and specificity were 97% for parkinsonism and 100% for ET in the group of the “institutional readers”, while sensitivity was 95% and specificity 93% for the expert nuclear medicine group. This study underlined that 123I-ioflupane SPET is a valuable tool in the differential diagnosis of parkinsonism and ET and suggested that an expert panel for clinical diagnosis was not necessary. Cases of PD, ET and atypical parkinsonism are shown in Figure 2.

<p>| Table 3. SPET nigrostriatal radiotracers classified on the basis of theselective interaction. |
|-------------------------------------|----------------------------------------|---------------|</p>
<table>
<thead>
<tr>
<th>SPET radiotracers</th>
<th>Chemical structure</th>
<th>Interaction</th>
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<tbody>
<tr>
<td>123I-FP-CIT</td>
<td>I-2β-carbomethoxy-3β-(4-iodophenyl) tropane</td>
<td>Presynaptic Dopamine Transporter (DaT)</td>
</tr>
<tr>
<td>123I-IP</td>
<td>I-β-CIT</td>
<td>Postsynaptic D2 receptor</td>
</tr>
<tr>
<td>123I-IBZM</td>
<td>2β-carbomethoxy-3β-(4-iodophenyl) nortropane</td>
<td>Postsynaptic D2 receptor</td>
</tr>
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Figure 1. Transaxial view of 123I-ioflupane SPET showing: a) a reduced tracer uptake in left putamen in PD, b) a homogeneous tracer uptake in AD and c) an irregular and pathological reduced tracer uptake in vascular parkinsonism.
Two hundred and seventy-three patients with clinically uncertain diagnosis were included in the study and were divided in two randomly selected groups. In 135 subjects, the diagnosis was based on both clinical examination and $^{123}$I-ioflupane SPET, while the remaining 138 were the control group for clinical evaluation. All patients were monitored for 12 months, after SPET imaging, with visits at weeks 4, 12, and 52. In all, at 52 weeks, there was a significant (P<0.001) difference in clinical diagnosis changes in the $^{123}$I-ioflupane SPET group (54%) with respect to the control one (23%). This data were also confirmed in the intermediate periods at four weeks (45% versus 9%; P<0.001) and at 12 weeks (46% versus 12%; P<0.001). The most important clinical impact derived by changing the diagnosis and was represented by the more confident management of dopaminergic treatment both in patients with abnormal and in those with normal SPET [22].

Iodine-123-ioflupane SPET evidenced an increased diagnostic confidence after imaging in 69% of patients with uncertain pS and a changing in treatment decision in 24% of cases [23]. This result has also been confirmed by a recent review study [24] which showed that $^{123}$I-ioflupane SPET provided useful information in nigrostriatal dopaminergic assessment, especially in cases with doubtful clinical signs of PD since this technique supported uncertain clinical diagnosis providing to discriminate nigrostriatal dopaminergic degeneration from non-nigrostriatal degeneration in these cases.

The ever-increasing importance of $^{123}$I-ioflupane SPET in clinical management of patients with parkinsonism has led to the publication of different guidelines in Europe and in the United States [25, 26]. Recently, the combined use of semi-quantitative analysis of $^{123}$I-ioflupane SPET uptake in basal ganglia has been suggested, since different studies have demonstrated its incremental value in respect of qualitative evaluation alone [27-31]; a large number of studies evidenced that the combined use of qualitative evaluation and semi-quantitative standardized analysis with fixed ROI led to a best intra and inter-observer agreement and to a more precise reproducibility of the method, thus providing more accurate correlations to clinical findings and reducing false positive results in patients with parkinsonism.

Different authors underlined that the semi-quantitative procedures offer a non-subjective evaluation overcoming the inter-observer variability [32, 33] and are recommended in those cases with unclear qualitative visual results such as a widespread irregular reduction of $^{123}$I-ioflupane uptake in the striatal nucleus or smaller differences at qualitative analysis between dementia and LBD [34] and between dementia of AD and of LBD [35]. The great variability in semi-quantitative analysis in different nuclear medicine centers, the low opportunity to compare patients data with matched normal controls as well as the limited availability of specific software for $^{123}$I-ioflupane uptake semi-quantification, have meant that for a long time there was not a unique use of $^{123}$I-ioflupane. Recently, some European multicenter studies, evaluating large series of patients and developing age-related references, suggested shared diagnostic methodologies. Furthermore, the availability of commercial software has led to better standardized semi-quantification of $^{123}$I-ioflupane SPET procedures so that the clinical use of semi-quantitative analysis of $^{123}$I-ioflupane SPET procedures...
titative analysis is now of greater importance specifically using nigrostriatal dopamine terminal imaging with DaT SPET [36]. In particular, the 'BasGan V2' software developed by the multicenter 'ENC-DAT' studies promoted by the EANM [37, 38], with the 3D ROI semi-quantitative analysis, in a large number of healthy subjects studied as controls allowed to calculate automatically the specific binding ratio (SBR) of $^{123}$I-ioflupane in caudate and putamen nuclei. Furthermore, these studies evidenced an existing correlation between age and expression of DaT receptors on the presynaptic membrane as well as between gender and DaT variations. Moreover, a direct dependence of SBR to body mass index, handedness, circadian rhythm of DaT regulation or season was not demonstrated.

Other authors [39, 40] recently have studied the effects of age and gender on striatal and extra-striatal $^{123}$I-ioflupane binding in PD, evaluating 231 PD patients with 230 normal controls. In this study, an automated region-of-interest based method (BRASS automated analysis software) for striatal nuclei and a voxel-based method (Statistical parametric mapping software, SPMS) for the entire brain were applied and no clear evidence of aging effect in radiotracer binding was demonstrated in PD patients, while $^{123}$I-ioflupane uptake was correlated both with age and gender in normal controls. Gender seemed to influence DaT expression since higher levels of dopamine transporter binding in caudate nucleus were observed in female subjects compared with males both in normal and in PD subjects. In striatal ROI, female subjects had 7.1%-21.1% higher binding of $^{123}$I-ioflupane in the caudate nuclei (P<0.0001) and this difference was nearly significant in the right posterior putamen. When PD and control groups were studied separately, female PD patients had higher binding compared with male PD patients in the right (mean [95% confidence interval], 2.47 [2.38e2.57] vs. 2.14 [2.05e2.23], P<0.0001) and left (2.55 [2.46e2.65] vs. 2.28 [2.19e2.38], P<0.001) caudate nuclei, and female controls had higher binding compared with male controls in the right (2.81 [2.71e2.90] vs. 2.57 [2.48e2.66], P<0.0001) and left (2.90 [2.80e3.00] vs. 2.71 [2.61e2.81], P<0.001) caudate and in the right posterior putamen (2.45 [2.36e2.54] vs. 2.30 [2.22e2.39], P<0.009). It may be also underlined that, the control subjects of the study included patients with ET, dystonia, and drug-induced parkinsonism and the results of the control group should not be interpreted as findings in healthy individuals but in individuals with normal striatal dopamine function.

Another issue emerging from the literature is the need to establish a threshold value of the $^{123}$I-ioflupane striatal uptake in semi-quantitative analysis in order to better differentiate normal from pathologic $^{123}$I-ioflupane binding levels [40].

The use of neural networks in the evaluation of $^{123}$I-ioflupane SPET semi-quantitative analysis, suggested by some authors [41], contributed to the differential diagnosis of PD and ET and confirmed the significant role of semi-quantitative analysis of $^{123}$I-ioflupane uptake in PD clinical management. Two different “artificial neural network automatic classifiers”, the probabilistic neural network (PNN) and the classification tree (CIT) were applied to define the statistical probability of a correct clinical differential diagnosis. For PNN, for early and advanced PD, the probability of correct classification was 81.9%±8.1% and 78.9%±8.1%, respectively, while it was 96.6%±2.6% for ET patients. For CIT, the first decision rule gave a mean value for the putamen of 5.99 that resulted in a probability of correct classification of 93.5%±3.4%.

These data suggest that different clinical features could be obtained when the binding levels of each striatal nucleus were evaluated separately. According to CIT results and considering the binding value of 5.99 as cut-off, patients with putamen values >5.99 were classified as ET, while those with putamen values <5.99 were automatically classified as PD; moreover, when the caudate nucleus value was higher than 6.97, the patients were classified as early PD (probability 69.8%±5.3%), while, if the binding value was <6.97, the patients were classified as advanced PD (probability 88.1%±8.8%). Furthermore, the two artificial classifiers may be useful in different clinical phases since it was found that PNN achieved valid classification results, while CIT provided reliable cut-off values able to differentiate ET from PD as well as to give accurate data on disease severity.

The semi-quantitative analysis of $^{123}$I-ioflupane SPET was recently analyzed in a multicenter study [42] that compared the data of different Centers and assessed the accuracy of the methods identifying the best threshold levels in order to obtain a unique reliable cut-off value for $^{123}$I-ioflupane caudate and putamen uptakes with high sensitivity and specificity values (86% and 89%, respectively). The authors suggested that standardized and shared $^{123}$I-ioflupane brain SPET semi-quantitative analysis represents the best condition to support clinical diagnosis in patients related to putamen uptakes.

Other authors investigated the performance of $^{123}$I-ioflupane brain SPET semi-quantitative analysis in patients with suspected PD by using a support vector machine classifier (SV-M), a powerful supervised classification algorithm. They evidenced that putamen uptake value of $^{123}$I-ioflupane, as evaluated by Bas Gan V2 software, was the most discriminative descriptor for PD and that the age of the patients influenced classification accuracy [43].

The use of the artificial intelligence was also recently suggested in neurodegenerative disorders [44]. The increasing role of machine learning was shown by an interesting recent study [45] comparing three machine learning algorithms with semi-quantification methods applied on 209 healthy controls and 448 patients with PD downloaded from the Parkinson’s progression marker initiative (PPMI) research database and from the local clinical database (Sheffield Teaching Hospitals NHS Foundation Trust) for validation. Machine learning algorithms were based on support vector machine classifiers with three different sets of features (voxel intensities, principal components of image voxel intensities and striatal binding ratios from the putamen and caudate), while semi-quantification methods were based on striatal binding ratios (SBR) from putamen, with and without considering caudate nuclei. The mean accuracy of the semi-quantitative methods to classify local data in parkinsonian and in non-parkinsonian groups ranged from 0.78 to 0.87, while varied from 0.89 to 0.95 in classifying healthy and PD subjects when PPMI data were considered. The machine learning algorithms provided mean accuracies ranging from 0.88 to 0.92 and 0.95 to
0.97 for local clinical database and PPMI data, respectively. The authors concluded that classification performance was lower for the local database than the research database for both semi-quantitative and machine learning algorithms. For both databases machine-learning methods provided similar or higher mean accuracies (with lower variance) comparing with any of the semi-quantification methods, but advantage in performance using machine-learning algorithms compared with semi-quantification methods was relatively small and may be insufficient, if considered in isolation, to improve clinical diagnosis.

Alzheimer's and Lewi's bodies dementia

In some postmortem studies it has been evidenced that the “in vivo” clinical differentiation between LBD and AD was often difficult, despite that in LBD cases there was a high percentage of presynaptic dopamine transporter damage (57%-90%) compared to AD cases [46, 47]. Therefore, the use of PET and SPET dopaminergic tracers that evidenced the presence of striatal dopaminergic transporter abnormalities was suggested [48] and recently 123I-ioflupane brain SPET was included as indicative biomarker for LBD in the revised clinical consensus criteria of LBD [49].

A recent Cochrane review [50] evidenced that only one study used a neuropathological reference standard to assess the accuracy of DAT imaging for the diagnosis of LBD, although for the small size of the included studies, sensitivity and specificity values were imprecise. However, the above study showed that DAT imaging was more accurate than clinical diagnosis. Moreover, the authors documented that no studies using a neuropathological reference standard, directly showed that DAT imaging was a diagnostic test for possible LBD patients or for accurate diagnosis of subjects with mild dementia. Finally, the data from the included above studies suggested that, if a patient had a moderately severe dementia and preexisting suspicion of LBD (probable LBD), a normal 123I-ioflupane brain SPET scan might be valuable to exclude LBD. Furthermore, semi-quantitative ratings of 123I-ioflupane brain SPET were more accurate than visual analyses.

Summing the above

In general, 123I-ioflupane SPET functional neuroimaging, with qualitative and semi-quantitative analyses [51], usually represents a useful tool both in PD and LBD initial diagnosis [52, 53] and in the differential diagnosis of uncertain parkinsonism [54, 55] since the procedure evaluates the DaT assessment with high specificity.

However, false positive results could be obtained with 123I-ioflupane SPET, especially in the differential diagnosis of PD from vascular parkinsonism (VP) and of LBD from AD when vascular lesions in basal ganglia occur. It was observed that some VP patients with vascular damage and unilateral disease had asymmetrical tracer striatal uptake similar to that evidenced in PD cases, probably due to the limited tracer possibility to arrive to the binding sites [56]. Therefore, PD diagnosis could be excluded when 123I-ioflupane SPET was normal, but remained unclear when a reduced tracer uptake occurred, thus leading to a diagnostic overlap.

In PD, vascular lesions are mainly in the striatal nuclei, but also in the white matter and this disease is considered a distinct clinical entity [3, 57]. Its differential diagnosis from other pS is a crucial clinical point because differs in progression, correct treatment strategy, potential supportive therapy and prognosis [58, 59]. The diagnostic criteria for suspected VP included clinical symptoms, or the exclusion of PD and pS and the exclusion of causes of secondary parkinsonism while hypertensive cerebral vascular disease or previous history of transient ischemic attack or stroke, even if expected, were not considered as important diagnostic parameters [60].

Magnetic resonance imaging

Although brain structural magnetic resonance imaging (MRI) is able to report brain vascular injuries, it is considered a supportive but not conclusive tool for confirming clinical diagnosis, since a specific pattern for VP has not yet been identified by MRI. Some authors have underlined that ischemic brain lesions could be evidenced by MRI both in VP and PD cases [57, 61, 62] as well as in AD [63] or in normal aged people with cardiovascular diseases or hypertension [64].

The use of 123I-metaiodobenzylguanidine cardiac scintigraphy

Recently, the combined use of 123I-ioflupane brain SPET and 123I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy is suggested in PD, pD, AD, LBD and other diseases (Figure 3).

Iodine-123-MIBG is considered a non-invasive useful method to evaluate postganglionic presynaptic cardiac sympathetic innervation [65, 66]. This radiopharmaceutical is an analogue of the adrenergic blocking agent guanethidine and has the same chemical structure of norepinephrine; the chemical structure of the tracer allows its detection with an active mechanism by postganglionic presynaptic fibers, the storage in synaptic vesicles and the release during nerve excitement with the same mechanism of noradrenaline. On the other hand, unlike of noradrenaline, 123I-MIBG is not bound to cardiac receptors and is not degraded by the enzymatic systems COMT and MAO, but it is reabsorbed in the presynaptic side and accumulated in the vesicles of nerve endings for a long time. Therefore, 123I-MIBG represents the ideal radiotracrer for the “in vivo” cardiac sympathetic system evaluation (Figure 3).

It was observed that the denervation damage well correlates with the early 123I-MIBG cardiac uptake, while the sympatheticotonia could be represented by the tracer wash-out and directly expressed by the evaluation of its delayed phase [66].

Cardiac scintigraphy by 123I-MIBG was originally used to evaluate the presynaptic postganglionic endings of sympathetic system in a large number of cardiac diseases, such as congestive heart failure, ischemic heart disease and cardiomyopathy [67-71].

Later this procedure was applied in the diagnosis of PD [72] (Figure 4) and in the differential diagnosis of this disease from other neurodegenerative disorders, such as MSA, PSP CBD [70, 73] and VP [74, 75]. This procedure was also used as indicative biomarker in the diagnosis of probable/possible LBD [49, 76].

Recently, some authors evaluated the usefulness of 123I-ioflupane brain SPET and 123I-MIBG cardiac scintigraphy in patients with suspected LBD [77]. For 123I-MIBG scintigraphy, the overall sensitivity, specificity, accuracy, positive and neg-
gative predictive values in LBD were 83%, 79%, 82%, 86% and 76%, respectively. For $^{123}$I-ioplaune SPET, the overall sensitivity, specificity, accuracy, positive and negative predictive values in LBD were 93%, 41%, 73%, 71% and 80%, respectively. The authors confirmed that LBD usually presents both myocardial sympathetic and striatal dopaminergic impairments, corresponding to abnormal $^{123}$I-MIBG scintigraphy and to $^{123}$I-ioplaune SPET, respectively. Moreover, the same authors found that $^{123}$I-ioplaune SPET seemed to detect LBD better than $^{123}$I-MIBG scintigraphy, due to its higher sensitivity (93% vs. 83%). On the contrast, $^{123}$I-MIBG scintigraphy seemed to exclude LBD better than $^{123}$I-ioplaune SPET, due to its higher specificity (79% vs. 41%), thus suggesting the complementary role of the two scintigraphic methods.

Other authors studied 133 patients with suspected AD or LBD. The sensitivity and specificity of differentiating LBD from AD were 72.4% and 94.4% for $^{123}$I-MIBG scintigraphy, 88.2% and 88.9% for $^{123}$I-ioplaune SPET, and 96.1% and 90.7% for combining both, respectively. These results suggested that the combined use of the two scintigraphic methods is more useful in practical approach to differentiate LBD from AD [78].

The usefulness of $^{123}$I-ioplaune SPET and $^{123}$I-MIBG cardiac scintigraphy combined use in clinical practice was recently further evaluated in clinically uncertain parkinsonian conditions associated to vascular cerebral lesions ascertained at MRI [79]. When vascular lesions in striatal nuclei and in white matter occur, brain $^{123}$I-ioplaune SPET alone was not able to discriminate between the different forms of disease. Only with $^{123}$I-MIBG cardiac scintigraphy association, it was possible to achieve the most appropriate diagnosis in 90.69% of cases. These data, in accordance with other authors [80] suggested a wider employment of these two procedures combined and especially in uncertain PD with ascertained striatal vascular damage and in particular, in AD/LBD differential diagnosis.

In conclusion, $^{123}$I-ioplaune SPET is useful in the diagnosis of PD and in other parkinsonian neurodegenerative diseases associated with dementia, especially in the early phases of these diseases and in differential diagnosis of AD and LBD. Iodine-123-ioplaune brain SPET and $^{123}$I-MIBG cardiac scintigraphy seem to be also useful in diagnosis and in differential diagnosis of AD and LBD.

The authors declare that they have no conflicts of interest.

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