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

Susanna Nuvoli[1] MD, Barbara Palumbo[2] MD, Simona Malaspina[3] MD, Giuseppe Madeddu[1] MD, Angela Spanu[1] MD

1. Unit of Nuclear Medicine, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy
2. Section of Nuclear Medicine and Health Physics, Department of Surgical and Biomedical Sciences, University of Perugia, Perugia, Italy
3. Unit of Nuclear Medicine, ASST Santi Paolo e Carlo and Department of Health Sciences, University of Milan, Milan, Italy

Keywords: ^{123}I-ioflupane SPET -^{123}I-MIBG cardiac scintigraphy -Dementias -Parkinsonism -Alzheimer's disease -Dementia with Lewy bodies

Corresponding author:
Dr Susanna Nuvoli MD,
Agg. Professor,
Unit of Nuclear Medicine,
Department of Clinical and Experimental Medicine,
University of Sassari, Viale San Pietro 8, 07100 Sassari, Italy.
Tel number: +39079228496/ +393381553103
Fax number: +39079228208.
snuvoli@uniss.it

Received:
8 February 2018
Accepted revised :
26 February 2018

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-ioflupane studied by single photon emission tomography (^{123}I-ioflupane SPET) and of ^{123}I-metaiodobenzylguanidine (^{123}I-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.

Hell J Nucl Med 2018; 21(1): 60-68 *Epub ahead of print: 20 March 2018* *Published online: 25 April 2018*

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].

Table 1. *Diseases related to Parkinson's disease.*

Classification	Example
Primary degenerative parkinsonism	a) Idiopathic Parkinson's disease (sporadic and genetic) b) Primary atypical degenerative parkinsonism 1. Progressive supranuclear palsy 2. Multiple system atrophy 3. Corticobasal degeneration 4. Parkinsonism dementia 5. Lewy bodies dementia
Secondary acquired parkinsonism	1. Drugs Induced: Antipsychotics such as dopamine receptors blocking drugs, antiemetics such as metoclopramide, dopamine depleting drugs like reserpine, tetrabenzine, alpha-methyldopa, lithium, flunarizine, cinnarizine. 2. Infectious: Post encephalitic 3. Toxins: MPTP, CO, Mn, Hg, CS2 4. Vascular: multi-infarct state of brain 5. Trauma: Pugilistic encephalopathy 6. Hemi atrophy hemi parkinsonism 7. Brain tumors in certain locations such as basal ganglia 8. Hydrocephalus 9. Hypoxia 10. Metabolic
Familial neurodegenerative disease causing parkinsonism	1. Huntington's disease 2. Wilson's disease 3. Hallervorden-Spatz disease 4. Olivopontocerebellar and spinocerebellar degeneration 5. Familial basal ganglia calcification 6. Familial Parkinsonism with peripheral neuropathy 7. Neuroacanthocytosis

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].

Table 2. *Etiopathogentic classification of parkinsonian disorders.*

Classification	Diseases
Degenerative parkinsonism	
Alpha-synuclein	Parkinson's disease Lewy bodies dementia Multiple system atrophy
Tau	Progressive supranuclear palsy Corticobasal degeneration Parkinson dementia complex
Non degenerative parkinsonism	
Vascular toxic	vascular parkinsonism MPPTP, Manganese poisoning
Drug infections	Antipsychotic treatment Postencephalitic parkinsonism

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 ^{123}I-ioflupane brain SPET and the postganglionic presynaptic cardiac sympathetic innervation using ^{123}I-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 ^{123}I-ioflupane SPET and ^{123}I-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).

Table 3. *SPET nigrostriatal radiotracers classified on the basis of theselective interaction.*

SPET radiotracers	Chemical structure	Interaction
^{123}I-FP-CIT (^{123}I-ioflupane)	^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane	Presynaptic Dopamine Transporter (DaT)
^{123}I-β-CIT	^{123}I-2β-carbomethoxy-3β-(4-iodophenyl) tropane	
^{123}I-IP	^{123}I-N-(3-iodopropen-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane	
^{99m}Tc-TRODAT-1	^{99m}Tc-[2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo [1–3] oct-2-yl]methyl](2-mercaptoethyl)amino] ethyl]amino]ethanethiolato(3-)-N2,N2′,S2,S2′]oxo-[1R-(exoexo)]	
^{123}I-IBZM	^{123}I-(S)-(-)-2-hydroxy-3-iodo-6-methoxy-N-([1-ethyl-2-pyrrolidyl]-methyl)benzamide)	Postsynaptic D2 receptor
^{123}I-IBF	^{123}I-(S)-5-iodo-7-N-[(1-ethyl-2-pyrrolidinyl) methyl]carboxamido-2,3- dihydrobenzofuran	
^{123}I-epidepride	^{123}I-(S)-N-((1-ethyl-2-pyrrolidinyl)methyl)-5-iodo-2,3-dimethoxybenzamide	

^{123}I-ioflupane brain SPET

Among the DaT radiotracers, ^{123}I-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 DaT and serotonin transporter (SERT) (2.8/1) receptors and 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 ^{123}I-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 ^{123}I-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 ^{123}I-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.

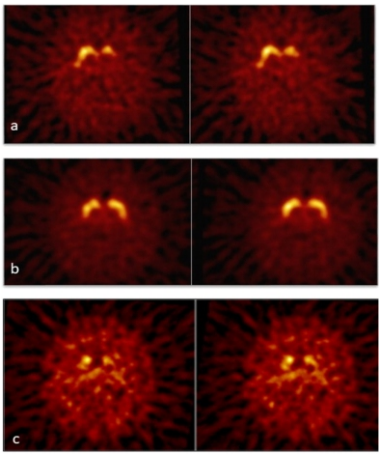

Figure 1. Transaxial view of ^{123}I-ioflupane SPET showing: a) a reduced tracer uptake in left putamen in PD, b) a homogeneous tracer uptake in AD and c) an irregular and pathological reduced tracer uptake in vascular parkinsonism.

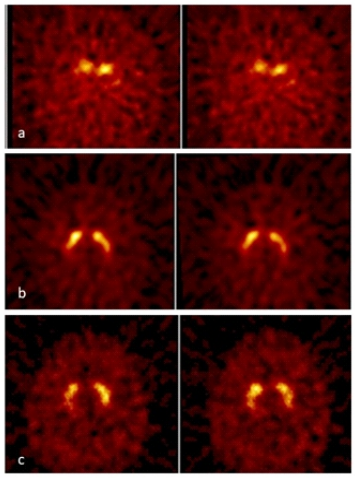

Figure 2. Transaxial view of ^{123}I-ioflupane SPET showing: a) Global reduced tracer uptake in both caudate and putamen nuclei in advanced PD, b) Homogeneous tracer uptake in essential tremor and c) Irregular and pathological reduced tracer uptake in atypical parkinsonism (Multiple System Atrophy).

Another study evaluated the effectiveness of ^{123}I-ioflupane imaging in supporting the differential diagnosis of pS [16]. The authors compared the accuracy of clinical diagnosis performed by movement disorder specialists with the ^{123}I-ioflupane SPET imaging results in thirty-five patients with suspected pS after an adequate follow-up. They found that clinical examination alone had high sensitivity but low specificity (92% vs 30%); thus, a large number of pS patients were misclassified as PD at first diagnosis. On the other hand, ^{123}I-ioflupane SPET allowed, already at the baseline examination, high sensitivity and specificity, thus confirming that ^{123}I-ioflupane SPET represents a useful diagnostic tool in differentiating PD from other movement disorders as already at the first examination.

The high diagnostic sensitivity and specificity of ^{123}I-ioflupane SPET was also confirmed by other authors [17]. They compared the results obtained by blinded imaging physicians and clinical trained experts who reviewed the videotapes of one hundred ninety-nine uncertain PD patients and three healthy volunteers with at 3 years follow-up in order to confirm clinical diagnosis; the diagnostic sensitivity and specificity by the neurologists was 93% and 46%, respectively, while by the ^{123}I-ioflupane SPET imaging was 78% and 97 %, respectively.

The usefulness ^{123}I-ioflupane SPET was also evidenced in a large number of movement disorders diagnosis such as action tremor [18] but the most appropriate use was for the clinical management of uncertain pS [19, 20]. Tracer usefulness was evidenced in a multicenter, open-label 2 years follow-up study of clinically uncertain pS [21]. At the 2 years follow-up of 85 patients, the rate of concordance between follow-up diagnosis and initial clinical diagnosis at baseline before ^{123}I-ioflupane SPET was 56%, thus suggesting a change in clinical diagnosis in 44% of patients.

The diagnostic accuracy of ^{123}I-ioflupane SPET was also assessed in a recent randomized study that evaluated the impact of the procedure on clinical disease management [22]; two hundred and seventy three patients with clinically uncertain pS 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 ($P<0.01$) 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-quan-

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 (ClT) 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 ClT, 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 ClT 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 affected by 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 ClT 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 (SVM), 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 da-ta 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 ^{123}I-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 pre-existing suspicion of LBD (probable LBD), a normal ^{123}I-ioflupane brain SPET scan might be valuable to exclude LBD. Furthermore, semi-quantitative ratings of ^{123}I-ioflupane brain SPET were more accurate than visual analyses.

Summing the above

In general, ^{123}I-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 ^{123}I-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 ^{123}I-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 ^{123}I-metaiodobenzylguanidine cardiac scintigraphy

Recently, the combined use of ^{123}I-ioflupane brain SPET and ^{123}I-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, ^{123}I-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, ^{123}I-MIBG represents the ideal radiotracer for the "in vivo" cardiac sympathetic system evaluation (Figure 3).

It was observed through that the denervation damage well correlates with the early ^{123}I-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 ^{123}I-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 ^{123}I-ioflupane brain SPET and ^{123}I-MIBG cardiac scintigraphy in patients with suspected LBD [77]. For ^{123}I-MIBG scintigraphy, the overall sensitivity, specificity, accuracy, positive and ne-

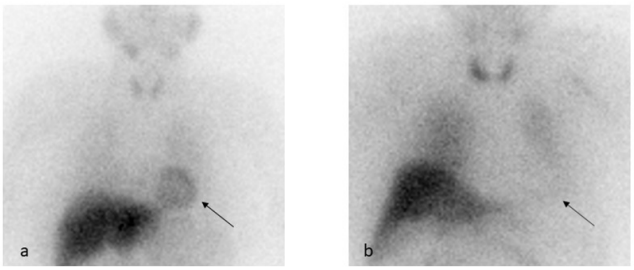

Figure 3. Planar anterior views of ^{123}I-MIBG cardiac scintigraphy showing: a) Normal homogeneous uptake in AD and b) Pathologically reduced tracer uptake in LBD (arrows).

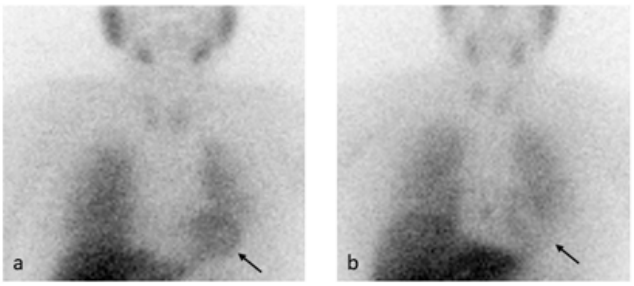

Figure 4. Planar anterior views of ^{123}I-MIBG cardiac scintigraphy showing: a) Normal homogeneous uptake in atypical parkinsonism (progressive supranuclear pulsy) and b) Pathologically reduced uptake in PD with dementia (arrows).

gative predictive values in LBD were 83%, 79%, 82%, 86% and 76%, respectively. For ^{123}I-ioflupane 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-ioflupane SPET, respectively. Moreover, the same authors found that ^{123}I-ioflupane 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-ioflupane 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-ioflupane 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-ioflupane 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-ioflupane 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 pS with ascertained striatal vascular damage and in particular, in AD/LBD differential diagnosis.

In conclusion, ^{123}I-ioflupane 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-ioflupane 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.

Bibliography

1. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. *Cold Spring Harb Perspect Med* 2012; 2(8). pii: a009258.
2. Moussaud S, Jones DR, Moussaud-Lamodière EL et al. Alpha-synuclein and tau: teammates in neurodegeneration? *Mol Neurodegener* 2014; 9: 43.
3. Quinn N. Parkinsonism-recognition and differential diagnosis. *BMJ* 1995; 310: 447-52.
4. Catafau AM, Tolosa E. Impact of Dopamine Transporter SPECT Using ^{123}I-Ioflupane on Diagnosis and Management of Patients with Clinically Uncertain Parkinsonian Syndromes. *Mov Disord* 2004 Oct;19(10):1175-82.
5. Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. *Lancet Neurol* 2006; 5(1): 75-86.
6. Ling H, O'Sullivan SS, Holton JL et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* 2010; 133 (Pt 7): 2045-57.
7. Palumbo B, Buresta T, Nuvoli S et al. SPECT and PET Serve as Molecular Imaging Techniques and in Vivo Biomarkers for Brain Metastases. *Int J Mol Sci* 2014; 15(6): 9878-93.
8. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015; 386 (9996): 896-912.
9. Garcia-Ruiz PJ, Espay AJ. Parkinson Disease: An evolutionary Perspective. *Front Neurol* 2017; 8: 157.
10. Arbizu J, Luquin MR, Abella J et al. Functional neuroimaging in the diagnosis of patients with Parkinsonism: Update and recommendations for clinical use. *Rev Esp Med Nucl Imagen Mol* 2014; 33(4): 215-26.
11. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev* 2011; 63(1): 182-217.
12. Nuvoli S, Spanu A, Madeddu G. Brain SPECT with Perfusion Radiopharmaceuticals and Dopaminergic System Radiocompounds in Dementia Disorders. *Curr Alzheimer Res* 2017; 14(2): 143-53.
13. Booij J, Hemelaar TG, Speelman JD et al. One-day protocol for imaging of the nigrostriatal dopaminergic pathway in Parkinson's disease by [^{123}I]FPCIT SPECT. *J Nucl Med* 1999; 40(5): 753-61.
14. Grosset DG, Tatsch K, Oertel WH et al. Safety analysis of 10 clinical trials and for 13 years after first approval of ioflupane ^{123}I injection (DaTscan). *J Nucl Med* 2014; 55(8): 1281-7.
15. Benamer TS, Patterson J, Grosset DG et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [^{123}I]-FP-CIT study group. *Mov Disord* 2000; 15(3): 503-10.
16. Jennings DL, Seibyl JP, Oakes D et al. (^{123}I) beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. *Arch Neurol* 2004; 61(8): 1224-9.
17. Marshall VL, Reininger CB, Marquardt M et al. Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [^{123}I]FP-CIT SPECT. *Mov Disord* 2009; 24(4): 500-8.
18. Niccoli Asabella A, Gigante AF, Ferrari C et al. Role of dopaminergic neurotransmission in pathophysiology of action tremor in Parkinson's disease. *Hell J Nucl Med* 2015; 18 Suppl 1: 11-6.
19. Seifert KD, Wiener JI The impact of DaTscan on the diagnosis and ma-

nagement of movement disorders: A retrospective study. *Am J Neurodegener Dis* 2013; 2(1): 29-34.
20. Bajaj N, Hauser R A, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (^{123}I) ioflupane in diagnosis of parkinsonian syndromes. *J Neurol Neurosurg Psychiatry* 2013; 84(11): 1288-95.
21. Tolosa E, Borght TV, Moreno. Accuracy of DaTSCAN (^{123}I-Ioflupane) SPECT in Diagnosis of Patients with Clinically Uncertain Parkinsonism: 2-Year Follow-Up of an Open-Label Study. *Movement Disorders* 2007; 22 (16): 2346-51.
22. Kupsch AR, Bajaj N, Weiland F et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. *J Neurol Neurosurg Psychiatry* 2012; 83(6): 620-8.
23. Covington MF, Sherman S, Lewis D et al. Patient Survey on Satisfaction and Impact of ^{123}I-Ioflupane Dopamine Transporter Imaging. *PLoS One* 2015; 10(7): e0134457.
24. Isaacson SH, Fisher S, Gupta F et al. Clinical utility of DaTscanTM imaging in the evaluation of patients with parkinsonism: a US perspective. *Expert Rev Neurother* 2017; 17(3): 219-25.
25. Darcourt J, Booij J, Tatsch K et al. EANM procedure guidelines for brain neurotransmission SPECT using ^{123}I-labelled dopamine transporter ligands, version 2. *Eur J Nucl Med Mol Imaging* 2010; 37(2): 443-50.
26. Djang DS, Janssen MJ, Bohnen N et al. SNM practice guideline for dopamine transporter imaging with ^{123}I-ioflupane SPECT. *J Nucl Med* 2012; 53(1): 154-63.
27. Filippi L, Manni C, Pierantozzi M et al. ^{123}I-FP-CIT semi-quantitative SPECT detects preclinical bilateral dopaminergic deficit in early Parkinson's disease with unilateral symptoms. *Nucl Med Commun* 2005; 26 (5): 421-6.
28. Stokkel MP, Dibbets-Schneider P, Koestering E et al. Reproducibility of a standardized quantitative analysis using fixed regions of interest to differentiate movement disorders on ^{123}I-FP-CIT SPECT. *J Nucl Med Technol* 2007; 35(1): 21-6.
29. Goethals I, Dobbeleir A, Ham H et al. Validation of a resolution-independent method for the quantification of ^{123}I-FP-CIT SPECT scans. *Nucl Med Commun* 2007; 28(10): 771-4.
30. Tossici-Bolt L, Hoffmann SM, Kemp PM et al. Quantification of [^{123}I]FP-CIT SPECT brain images: an accurate technique for measurement of the specific binding ratio. *Eur J Nucl Med Mol Imaging* 2006; 33(12): 1491-9.
31. Calvini P, Rodriguez G, Inguglia F et al. The basal ganglia matching tools package for striatal uptake semi-quantification description and validation. *Eur J Nucl Med Mol Imaging* 2007; 34(8): 1240-53.
32. Scherfler C, Nocker M. Dopamine transporter SPECT: how to remove subjectivity? *Mov Disord* 2009; 24 Suppl 2: S721-4.
33. Tondeur MC, Hambye AS, Dethy S, Ham HR. Interobserver reproducibility of the interpretation of I-123 FP-CIT single-photon emission computed tomography. *Nucl Med Commun* 2010; 31(8): 717-25.
34. Walker Z, Jaros E, Walker RW et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *J Neurol Neurosurg Psychiatry* 2007; 78(11): 1176-81.
35. Walker Z, Costa DC, Walker RW et al. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. *J Neurol Neurosurg Psychiatry* 2002; 73(2): 134-40.
36. Tatsch K, Poepperl G. Nigrostriatal dopamine terminal imaging with dopamine transporter SPECT: an update. *J Nucl Med* 2013; 54(8): 1331-8.
37. Nobili F, Naseri M, De Carli F et al. Automatic semi-quantification of [^{123}I]FP-CIT SPECT scans in healthy volunteers using BasGan version 2: results from the ENC-DAT database. *Eur J Nucl Med Mol Imaging* 2013; 40(4): 565-73.
38. Varrone A, Dickson JC, Tossici-Bolt L et al. European multicentre database of healthy controls for [^{123}I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. *Eur J Nucl Med Mol Imaging* 2013; 40(2): 213-27.
39. Kaasinen V, Joutsa J, Noponen T et al. Effects of aging and gender on striatal and extrastriatal [^{123}I]FP-CIT binding in Parkinson's disease. *Neurobiol Aging* 2015; 36(4): 1757-63.
40. Cascianelli S, Tranfaglia C, Fravolini ML et al. Right putamen and age are the most discriminant features to diagnose Parkinson's disease by using ^{123}I-FP-CIT brain SPET data by using an artificial neural network classifier, a classification tree (CIT). *Hell J Nucl Med* 2017; 20 Suppl: 165.
41. Palumbo B, Fravolini ML, Nuvoli S et al. Comparison of two neural network classifiers in the differential diagnosis of essential tremor and Parkinson's disease by (^{123})I-FP-CIT brain SPECT. *Eur J Nucl Med Mol Imaging* 2010; 37(11): 2146-53.
42. Skanjeti A, Castellano G, Elia BO et al. Multicenter Semiquantitative Evaluation of (^{123})I-FP-CIT Brain SPECT. *J Neuroimaging* 2015; 25(6): 1023-9.
43. Palumbo B, Fravolini ML, Buresta T et al. Diagnostic accuracy of Parkinson disease by support vector machine (SVM) analysis of ^{123}I-FP-CIT brain SPECT data: implications of putaminal findings and age. *Medicine (Baltimore)* 2014; 93(27): e228.
44. Cascianelli S, Scialpi M, Amici S et al. Role of Artificial Intelligence Techniques (Automatic Classifiers) in Molecular Imaging Modalities in Neurodegenerative Diseases. *Curr Alzheimer Res* 2017; 14(2): 198-207.
45. Taylor JC, Fenner JW. Comparison of machine learning and semi-quantification algorithms for (^{123}I)FP-CIT classification: the beginning of the end for semi-quantification? *EJNMMI Phys* 2017; 4(1): 29.
46. Piggott MA, Marshall EF, Thomas N et al. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. *Brain* 1999; 122(Pt 8): 1449-68.
47. Suzuki M, Desmond TJ, Albin RL, Frey KA. Striatal monoaminergic terminals in Lewy body and Alzheimer's dementias. *Ann Neurol* 2002; 51(6): 767-71.
48. Bittner V, Ullrich G, Thormann M et al. Positive FP-CIT SPECT (DaTSCAN) in Clinical Alzheimer's Disease - An Unexpected Finding? *Dement Geriatr Cogn Dis Extra* 2011; 1(1): 283-91.
49. McKeith IG, Boeve BF, Dickson DW et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017; 89(1): 88-100.
50. McCleery J, Morgan S, Bradley KM et al. Dopamine transporter imaging for the diagnosis of dementia with Lewy bodies. *Cochrane Database Syst Rev* 2015; 1: Cd010633.
51. Contrafatto D, Mostile G, Nicoletti A et al. [^{123}I]FP-CIT-SPECT asymmetry index to differentiate Parkinson's disease from vascular parkinsonism. *Acta Neurol Scand* 2012; 126(1): 12-6.
52. Kägi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. *J Neurol Neurosurg Psychiatry* 2010; 81(1): 5-12.
53. Zijlmans JC. The role of imaging in the diagnosis of vascular parkinsonism. *Neuroimaging Clin N Am* 2010; 20(1): 69-76.
54. Tolosa E, Borght TV, Moreno E. DaTSCAN Clinically Uncertain Parkinsonian Syndromes Study Group. Accuracy of DaTSCAN (^{123}I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. *Mov Disord* 2007; 22(16): 2346-51.
55. Suwijn SR, van Boheemen CJ, de Haan RJ et al. The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review. *EJNMMI Res* 2015; 5: 12.
56. Gupta D, Kuruvilla A. Vascular parkinsonism: what makes it different? *Postgrad Med J* 2011; 87(1034): 829-36.
57. Demirkiran M, Bozdemir H, Sarica Y. Vascular parkinsonism: a distinct, heterogeneous clinical entity. *Acta Neurol Scand* 2001; 104(2): 63-7.
58. Thanvi B, Lo N, Robinson T. Vascular parkinsonism-an important cause of parkinsonism in older people. *Age Ageing* 2005; 34(2): 114-9.
59. Schrag A, Ben-Shlomo Y, Quinn N. How valid is the clinical diagnosis of Parkinson's disease in the community? *J Neurol Neurosurg Psychiatry* 2002; 73(5): 529-34.
60. Zijlmans JC, Daniel SE, Hughes AJ et al. Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. *Mov Disord* 2004; 19(6): 630-40.
61. Piccini P, Pavese N, Canapicchi R et al. White matter hyperintensities in Parkinson's disease. Clinical correlations. *Arch Neurol* 1995; 52(2): 191-4.
62. Rampello L, Alvano A, Battaglia G et al. Different clinical and evolutional patterns in late idiopathic and vascular parkinsonism. *J Neurol* 2005; 252(9): 1045-9.
63. Appel J, Potter E, Shen Q et al. A comparative analysis of structural brain MRI in the diagnosis of Alzheimer's Disease. *Behav Neurol* 2009; 21 (1): 13-9.
64. Jeerakathil T, Wolf PA, Beiser A et al. Stroke risk profile predicts white matter hyperintensity volume: the Framingham Study. *Stroke* 2004; 35(8): 1857-61.
65. Vallabhajosula S, Nikolopoulou A. Radioiodinated metaiodobenzylguanidine (MIBG): radiochemistry, biology, and pharmacology. *Semin*

Nucl Med 2011; 41(5): 324-33.
66. Yamashina S, Yamazaki J. Neuronal imaging using SPECT. *Eur J Nucl Med Mol Imaging* 2007; 34 Suppl 1: S62-73.
67. Flotats A, Carrió I, Agostini D et al. EANM Cardiovascular Committee; European Council of Nuclear Cardiology. Proposal for standardization of ^{123}I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. *Eur J Nucl Med Mol Imaging* 2010; 37(9): 1802-12.
68. Martins da Silva MI, Vidigal Ferreira MJ, Morão Moreira AP. Iodine-123-metaiodobenzylguanidine scintigraphy in risk stratification of sudden death in heart failure. *Rev Port Cardiol* 2013; 32(6): 509-16.
69. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial ^{123}I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. *Eur Heart J* 2008; 29(9): 1147-59.
70. Orimo S, Suzuki M, Inaba A, Mizusawa H. ^{123}I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: a systematic review and meta-analysis. *Parkinsonism Relat Disord* 2012; 18(5): 494-500.
71. Pace L, Betocchi S, Losi MA et al. Sympathetic nervous function in patients with hypertrophic cardiomyopathy assessed by [^{123}I]-MIBG: relationship with left ventricular perfusion and function. *Q J Nucl Med Mol Imaging* 2004; 48(1): 20-5.
72. Oka H, Toyoda C, Yogo M, Mochio S. Reduced cardiac 123I-MIBG uptake reflects cardiac sympathetic dysfunction in de novo Parkinson's disease. *J Neural Transm (Vienna)* 2011; 118(9): 1323-7.
73. Shin DH, Lee PH, Bang OY et al. Clinical Implications of Cardiac-MIBG SPECT in the Differentiation of Parkinsonian Syndromes. *J Clin Neurol* 2006; 2(1): 51-7.
74. Kim JS, Lee PH, Lee KS et al. Cardiac [^{123}I]metaiodobenzylguanidine scintigraphy for vascular Parkinsonism. *Mov Disord* 2006; 21(11): 19-90-4.
75. Kalra S, Grosset DG, Benamer HT. Differentiating vascular parkinsonism from idiopathic Parkinson's disease: a systematic review. *Mov Disord* 2010; 25(2): 149-56.
76. McKeith IG, Dickson DW, Lowe J et al. Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005; 65(12): 1863-72.
77. Treglia G, Cason E, Cortelli P et al. Iodine-123 metaiodobenzylguanidine scintigraphy and iodine-123 ioflupane single photon emission computed tomography in Lewy body diseases: complementary or alternative techniques? *J Neuroimaging* 2014; 24(2): 149-54.
78. Shimizu S, Hirao K, Kanetaka H et al. Utility of the combination of DAT SPECT and MIBG myocardial scintigraphy in differentiating dementia with Lewy bodies from Alzheimer's disease. *Eur J Nucl Med Mol Imaging* 2016; 43(1): 184-92.
79. Nuvoli S, Spanu A, Piras MR et al. ^{123}I-Ioflupane brain SPECT and ^{123}I-MIBG cardiac planar scintigraphy combined use in uncertain parkinsonian disorders. *Medicine (Baltimore)* 2017; 96(21): e6967.
80. Giza E, Gotzamani-Psarrakou A, Bostantjopoulou S. Imaging beyond the striatonigral dopaminergic system in Parkinson's disease. *Hell J Nucl Med* 2012; 15(3): 224-32.

Domenico Theotokopoulos-El Greco 1587-1592. Oil in canvas 121x105. Apostles Peter and Paul.