Presynaptic dopaminergic neuroimaging in REM sleep behavior disorder: a systematic review and meta-analysis.

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Conflict of interest

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Summary

The presence of polysomnography-confirmed REM sleep behavior disorder (RBD) is the stronger risk factor for having prodromal Parkinson disease (PD), followed by abnormal presynaptic dopaminergic radionuclide neuroimaging. Aim of the review is to conduct a meta-analysis of literature data regarding presynaptic dopaminergic neuroimaging in RBD.

A literature search was conducted, resulting in 16 papers that met the inclusion criteria. Clinical and neuroimaging data were extracted. The studies are heterogeneous, especially for neuroimaging methodology. Two mathematical transformations were used to allow imaging data to be compared among studies. Tracer uptake progressively decreased from controls to idiopathic RBD and eventually PD patients with RBD at putamen level. Tracer uptake at caudate level overlapped between patients with idiopathic RBD and those with PD without RBD. These results support the hypothesis that idiopathic RBD patients are on the path to developing a synucleinopathy. The receiver operation characteristic analysis found good to excellent discrimination capability between all groups.

Presynaptic dopaminergic neuroimaging may be a key feature in the stratification of subjects to be included in neuroprotective trials. However, literature data are heterogeneous. Multicentric, harmonized studies are needed to define the usefulness of presynaptic dopaminergic neuroimaging with the aim of testing neuroprotective trials for idiopathic RBD.

Introduction

REM sleep behavior disorder (RBD) is a parasomnia occurring during REM sleep; it is characterized by the loss of physiological muscle atonia and is associated with dream-enacted behaviors [1]. When the sleep disorder is isolated, without any clinical sign of a neurological disorder, it is named 'idiopathic' (iRBD). However, with an adequately long follow-up, more than 80% of iRBD patients will develop a definite neurodegenerative disease, mostly a synucleinopathy [2, 3]. Indeed, the presence of polysomnography-confirmed RBD is the stronger risk factor for having prodromal Parkinson disease (PD) [4]. According to the movement disorder society research criteria for prodromal PD, the second most relevant risk factor is the presence of abnormal presynaptic dopaminergic positron emission tomography (PET) or single photon emission tomography (SPECT) imaging [4]. Therefore, RBD and dopaminergic presynaptic radionuclide neuroimaging will likely be key features in the stratification of subjects to be included in future neuroprotective trials.

Our aim was to systematically review the available literature data regarding presynaptic dopaminergic radionuclide neuroimaging in RBD and to discuss its possible utility in the design of neuroprotective trials.

Methods

Search strategy

A comprehensive electronic literature search of the PubMed/MEDLINE, Embase and Scopus databases was conducted to find relevant published articles about the role of presynaptic radionuclide imaging in RBD. We used a search algorithm that was based on a combination of the following medical subject headings (MeSH): a) "REM sleep behavior disorder" and b) "SPECT", "single photon emission tomography", "PET" or "positron emission tomography". The publication dates of the articles retrieved ranged from 2000 to 2017; the search was updated until September 2017. Only articles in English were selected. To expand our search, the reference lists of the articles

retrieved by the electronic searches were reviewed to check for other relevant reports not indexed in the electronic database. Only *in extenso* published, peer-reviewed papers (i.e., not personal communications) were considered eligible for inclusion.

Study selection

Studies investigating the role of presynaptic dopaminergic imaging in RBD were eligible. Review articles, editorials or letters, case reports, conference proceedings and preclinical studies were excluded from this review. Two researchers (DA and MB) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria as above. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data extraction

Two authors (DA and MB) independently extracted data from each included study. Data extraction forms were used, and any discrepancies were resolved by mutual agreement. The raw form of the standardized binding ratio (SBR) SPECT/PET data was collected. Studies not reporting SBR SPECT/PET values of the patients were excluded from the study.

The following data were extracted: author(s); year of publication; inclusion criteria; number of subjects; age; gender; diagnosis (i.e., iRBD and/or PD); disease duration (years); Hoehn and Yahr stage; Unified Parkinson disease rating scale, motor section (UPDRS-III) scores; L-dopa equivalent doses; percentages of REM sleep without atonia (RWA); patients overlapping between studies; SPECT or PET device used; tracer administered; parts of the striatum evaluated; PET/SPECT SBRs; scan details; reconstruction algorithm; volume of interest (VOI) definition method; reference region used for normalization; formula used for normalization; VOI dimension; healthy control selection criteria; and cut-off used to define pathological findings.

Statistical analysis

A first, descriptive analysis was performed to investigate whether the study cohorts were clinically comparable between studies. Age, gender and inclusion/exclusion criteria were used for this purpose. Univariate analysis of variance (ANOVA) and chi-square tests were used to compare age and gender, respectively, between studies.

The second analysis was aimed at evaluating dopaminergic PET/SPECT data between studies. Since we lacked individual measures, the cohorts should be both statistically and clinically equivalent among all studies. Under this assumption, we might relate each cohort SBR measure in different studies as a particular sampling of a larger population and regard any major discrepancy as due to the different acquisition techniques (PET, SPECT), tracers used and quantification methods. However, this assumption was not true, particularly for age, in two studies [5, 6]. Thus, the cohorts were not equivalent among all studies. However, demographic data were not different between groups within all studies. That is, there were no significant differences in demographic data between the study groups (iRBD, PD or PDRBD) and the healthy controls used in each study. Thus, it is reasonable to compare imaging data from different studies with reference to healthy controls of the same study. Keeping this limitation in mind, we proceeded with the evaluation of dopaminergic PET/SPECT data.

Given the large heterogeneity in the reported measures, we considered only the SBR average values of the two putamen and the two caudate nuclei, computing the standard deviation accordingly. Studies lacking the standard deviation were assigned a fiducially value of x/sqrt(n), where x is the bilateral average of SBRs and n is the sample size. Salsone et al.'s study [7] was not included in this analysis because SPECT data of the whole striatum were reported instead of reporting the putamen and caudate nuclei data separately.

Considering that the studies differed significantly in sample size, number of groups, tracers, modalities and quantification analyses, they were not comparable between each other. Therefore,

we attempted to compare them using two approaches with the aim of providing an estimate of what a true multicentric study could deliver, should protocols and analyses be shared.

In the first approach, we normalized each study to the SBR value of the respective control group (SBR_patient/SBR_control). Here, we looked at the relative decrease in uptake (%) with respect to each study's own reference group. This analysis put all control group values equal to 100% by construction. This approach made the SBRs in patients comparable among studies, but it compressed the controls' natural variability into a single value.

The second approach instead tried to preserve the differences among studies and groups by mapping each study onto an equivalent SBR, which serves as a common reference. This latter approach is based on the assumption that there is a relationship among SBRs reported in all studies; that is, SBRs should be monotonic regardless of the acquisition method and analysis technique. The monotonicity in this context can be exemplified as follows: suppose, for instance, that there are two subjects, A and B, who both underwent two different analyses (i.e., ^{123}I-FP-CIT-SPECT and ^{18}F-DOPA-PET scans). Then, if SBR^^{123}I-FP-CIT-SPECT_A > SBR^^{123}I-FP-CIT-SPECT_B, it implies that SBR^^{18}F-DOPA-PET_A > SBR^^{18}F-DOPA-PET_B.

In addition, semiquantification analysis involves the ratio between an uptake VOI and a reference VOI. Even though the exact relationship between methods and techniques is unknown, it is reasonable to assume that this relationship is at least linear (that is, the first approximation of a monotonic function). At the least possible order then, we need to derive a proportionality constant among studies.

This approach is based on the assumption that the main source of discrepancy among the respective groups in different studies is due to technical heterogeneity (acquisition technique, radiotracer, and reconstruction and semiquantification protocols) rather than due to clinical ones (demographics and pathology severity). In other words, it is assumed that the respective groups in different studies are "clinically equivalent".

First, we noted that we could cluster studies based on groups' value compatibility. That is, there are studies for which results for the respective groups are generally within the confidence limits (+/- 3 standard deviations). This rule allowed us to partition all the studies into five clusters: a reference cluster consisting of six studies (hereafter named Reference) [8-13] and four others clusters (A, B, C and D) containing one to two studies (Figure 1).

For each cluster and cohort, we computed the weighted SBR average. We then fitted the proportion parameter k_[i,Ref] that mapped the SBRs average values of the cluster i onto those of the reference cluster SBRs, effectively leading to an equivalent SBR whose range is approximately equal to that of the reference cluster (SBR_i_equiv = k_[i,Ref] * SBR_i). A graphical representation of the proportionality constant is provided in Figure 2.

With this simple proportional approach, we could map all studies onto the same (equivalent) SBR range. The potential of this approach is that it preserves the variability of the control cohort and allows receiver operator characteristic (ROC) curves to be computed.

For this latter task, we observed that each point comes with a standard deviation (also linearly mapped together with the average value). Therefore, we could estimate the general cohort distribution as the weighted sum of the Gaussian distributions from each study, the weights being the study's number of subjects in that cohort. Once the overall cohort distribution is found, we can easily apply the ROC analysis.

Results

The search strategy yielded 88 studies. Among them, 19 studies were selected according to the preliminary inclusion and exclusion criteria. Three studies were excluded due to the absence of PET or SPECT data. Thus, 16 studies contributed to this review [5-20] (Figure 3), the earliest was published in 2000, and the most recent, in 2017. Detailed characteristics of the included studies are reported in Table 1 and Table 2. It has to be highlighted that there is a significant cohort overlap between studies of the same group, as seen in Table 1. When the overlap was complete, we

analyzed only the largest studies (for instance, we included in the analysis only study number 16 and not study numbers 6 and 8). In other studies, it was not possible to know the exact study overlap; thus, including some duplicated data was inevitable. Indeed, we analyzed data from 191 subjects, but we estimated that the real number should be approximately 180 subjects, with approximately 11 subjects with duplicated data. Even if it is a small proportion, these duplicated data may have biased our results. Only a true multicentric study would allow a correct estimation.

Statistical analysis

Age was significantly different between studies ($p<0.0001$ for healthy controls, iRBD and PD; $p<0.05$ for PD patients with RBD (PDRBD)) in all study cohorts mostly because of Wing et al.'s [5] and Zoetmulder et al.'s [6] studies. Indeed, in those studies, the mean age was significantly lower compared with those in the other studies as determined by post hoc comparisons ($p<0.01$). The gender of controls was significantly different between studies ($p=0.007$). This is mostly because in Arnaldi et al.'s [9] and Zoetmulder et al.'s [6] studies, healthy controls were balanced between males and females, while in the other studies, males were predominant. Indeed, excluding those two studies, gender was not significantly different between the remaining studies.

Inclusion and exclusion criteria, as well as diagnostic criteria, were homogeneous between studies. The only meaningful difference was that considering the studies involving PD patients, in Arnaldi et al. 2015a [8] and 2016 [10], only drug naïve, de novo PD patients were enrolled, while in the other studies, PD patients were under dopaminergic treatment and at different stages of the disease.

Figure 4 shows PET/SPECT data as they were reported. A trend of decreased putaminal and caudate uptake is seen in the four study groups. However, the studies are not comparable among each other due to methodological differences.

Figure 5 shows PET/SPECT data using the first approach showing the relative decrease in uptake, expressed as a percentage of each study's own reference group. A clear trend of decreased basal

ganglia uptake in the four groups is noticeable with this approach. However, the natural variability of the controls is compressed into a single value.

Figure 6 shows PET/SPECT data using the second proportional approach, showing again a clear trend of decreased putaminal uptake in the four study groups. Caudate uptake also progressively decreased from healthy controls to iRBD patients and from PD to PDRBD patients but without differences between iRBD and PD patients. This finding is also evident looking at the caudate/putamen ratio representation (Figure 6, bottom square).

Figure 7 shows the ROC curves, and Table 3 shows the area under the curve (AUC) obtained from the ROC analysis.

Discussion

Several studies have investigated presynaptic dopaminergic imaging in RBD, either idiopathic or associated with PD. Brain radionuclide dopaminergic presynaptic imaging techniques allow in vivo assessment of the nigro-striatal pathway integrity, playing a crucial role in the clinical diagnosis of PD [21]. Almost twenty years ago, the first study reported decreased dopaminergic innervation in iRBD [14]. Since then, this finding has been repeatedly confirmed in several independent cohorts and with different tracers. Indeed, the presence of abnormal presynaptic dopaminergic PET/SPECT imaging and of RBD are now considered the two most important risk factors for prodromal PD [4]. *Substantia nigra* impairment has been subsequently confirmed in iRBD patients by structural neuroimaging techniques [22-24]. Moreover, two recent studies have shown that iRBD patients with reduced nigro-striatal dopaminergic function are at high risk for short-term conversion into a synucleinopathy [20, 25]. Thus, RBD diagnosis and presynaptic dopaminergic dysfunction are likely to be two key markers able to identify patients eligible for neuroprotective trials. To this aim, markers should be feasible for application across multiple centers and thus need to be harmonized. The available literature data of presynaptic dopaminergic imaging in RBD are largely heterogeneous. First, a limited number of subjects have been investigated so far. Taking into

account all the studies included in the present meta-analysis, there are data available for only 191 iRBD subjects. However, considering that the studies overlap, the real number is even smaller. Although the exact overlap between studies cannot be computed, a rough estimation suggests that approximately 180 subjects have been investigated. Moreover, in addition to basic inclusion/exclusion criteria, the clinical characteristics of the subjects are largely unknown, as seen in Table 1. Furthermore, both age and gender are not homogeneous among studies.

Both neuroimaging techniques and tracers are widely variable between studies, with ^{123}I-FP-CIT-SPECT being the most common. The normalization methods used for data semiquantification are heterogeneous. Five of 16 studies have adopted semi-automatic quantification software [5, 6, 8-10]. The normalization reference region widely varied between studies, with the occipital cortex being the most common. Moreover, the normalization formulae used were heterogeneous. Finally, the VOI dimension was largely heterogeneous or not reported at all.

In summary, the published works appeared both clinically and technically heterogeneous. Thus, the harmonization needed for considering the use of presynaptic dopaminergic imaging in the design of neuroprotective trials in iRBD has not been achieved yet. Effort in conducting large, multicentric studies with shared clinical and technical parameters is strongly encouraged.

Keeping in mind the aforementioned limitations, we attempted to compare neuroimaging results between studies with two different methods. This approach would provide an estimate of what a true multicentric study could deliver if protocols and analyses were shared. SBRs progressively decreased from healthy controls to iRBD, PD and eventually PDRBD patients with both methods used (Figures 5 and 6), especially at the putamen level. This result supports the hypothesis that iRBD patients are on the path to developing a synucleinopathy.

Interestingly, SBR values at the caudate level largely overlapped between iRBD and PD without RBD patients. Indeed, caudate SBRs poorly differentiated between iRBD and PD without RBD patients at ROC analysis, while it efficiently differentiated iRBD from healthy controls (Figure 7 and Table 3). This finding is in line with the results of a previous study [8] in which the nigro-

caudate dopaminergic deafferentation was proposed as a marker of RBD. Indeed, iRBD patients as a group show a nigro-caudate dopaminergic impairment that is comparable to the one in patients with full-blown PD, despite the absence of any clinical neurological sign.

With the exception of the comparison between iRBD and PD, the ROC analysis found good to excellent discrimination capability between all the included groups, achieving nearly to perfect discrimination between healthy controls and PD patients with RBD (Table 3). It has to be highlighted that the presented analysis needed artificial mathematical transformation to allow the imaging data to be compared with each other.

In conclusion, considering the excellent results of the ROC analysis performed with the mentioned limitations, large, multicentric studies should be encouraged to harmonize acquisition and reconstruction protocols as well as semi-quantification procedures of presynaptic dopaminergic imaging in RBD. In the previous decade, the neuroimaging committee of the European Association of Nuclear Medicine launched a large European study for ^{123}I-Ioflupane SPECT acquisition harmonization, the ENC-DAT study [26]. This effort has generated calibration coefficients to be used with several of the gamma cameras on the market [27] as well as normal reference data with some free or commercial software [26, 28]. This large study has shown the reduced variability among centers provided that harmonized acquisition and reconstruction protocols are used [29-31]; however, not all centers use these procedures.

This approach would allow, for instance, the acquisition of clear cut-off values that are able to discriminate iRBD patients from healthy controls and possibly the accurate identification of those iRBD patients at high risk of conversion into a synucleinopathy. It has to be highlighted that approximately half of iRBD patients who eventually convert into a neurodegenerative disease, will develop dementia with Lewy bodies (DLB) instead of PD [32]. This is particularly relevant considering that DLB and PD patients exhibit different patterns of presynaptic dopaminergic SPECT alteration. Indeed, DLB patients show more severe nigro-caudate deafferentation than PD patients [33]. Thus, comparable caudate SBR in iRBD and PD groups as well as the flat

caudate/putamen ratio in the iRBD group (Figure 6) may indicate that a substantial number of RBD patients might be on the path toward prodromal DLB instead of prodromal PD. A harmonized, large, multicentric study may provide information allowing the identification of different patterns of presynaptic dopaminergic SPECT alteration possibly related to different iRBD clinical phenotypes. This approach may lead to better stratification of subjects to be included in future neuroprotective trials.

Practice points

1. Presynaptic dopaminergic radionuclide neuroimaging may be a key feature in the stratification of subjects to be included in neuroprotective trials.
2. Available literature data on presynaptic radionuclide neuroimaging in patients with REM sleep behavior disorder are largely heterogeneous, especially for neuroimaging methodology.
3. Patients with idiopathic REM sleep behavior disorder exhibits decreased nigro-striatal dopaminergic functioning in comparison with healthy controls, especially at the putamen level.
4. Patients with idiopathic REM sleep behavior disorder and patients with Parkinson disease without REM sleep behavior disorder exhibit a similar degree of nigro-caudate dopaminergic deafferentation.

Research agenda

Large, multicentric studies are needed to harmonize acquisition and reconstruction protocols as well as semi-quantification procedures of presynaptic dopaminergic radionuclide imaging in REM sleep behavior disorder. This approach may allow the following to occur:

1. Identification of clear cut-off values able to discriminate patients with idiopathic REM sleep behavior disorder from healthy controls.
2. Identification of those patients with idiopathic REM sleep behavior disorder at high risk of conversion into a synucleinopathy.
3. Identification of different patterns of presynaptic dopaminergic radionuclide neuroimaging alterations able to differentiate those patients with idiopathic REM sleep behavior disorder who will eventually develop Parkinson disease from those who will more likely develop dementia with Lewy bodies.

Figure legends

Figure 1. Clustering patterns of studies based on groups value compatibility. The first cluster represents the Reference group. The red horizontal lines show the weighted SBR average (per cohort and study cluster).

Figure 2. Graphical representation of the proportionality constant across clusters. The gray dotted line represents the k_[i,Ref] =1 reference linear function obtained from the Reference cluster (corresponds to no adjustment). The red line represents the linear function that is used to map each cohort of clusters A-D onto the reference one. The circles represent the weighted SBR averages for each groups and cluster.

Figure 3. Flow chart of the search strategy, retrieval and selection process.

Figure 4. Box plots of PET/SPECT presynaptic dopaminergic standardized binding ratios (SBRs) of the selected studies as they were reported.

Figure 5. Box plots of PET/SPECT presynaptic dopaminergic standardized binding ratios (SBRs) of the selected studies, expressed as percentages with respect to each study's own healthy control cohort.

Figure 6. Box plots of PET/SPECT presynaptic dopaminergic standardized binding ratios (SBRs) of the selected studies after proportional mapping.

Figure 7. Receiver operation characteristic (ROC) curves showing the estimated discrimination capability between groups of caudate and putamen SBRs.

References

1. Arnaldi D, Antelmi E, St Louis EK, Postuma RB, Arnulf I. Idiopathic REM sleep behavior disorder and neurodegenerative risk: To tell or not to tell to the patient? How to minimize the risk? Sleep Med Rev. 2017;36:82-95.

*2. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older males initially diagnosed with idiopathic REM sleep behavior disorder (RBD): 16year update on a previously reported series. Sleep Med. 2013;14(8):744-8.

*3. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Luis Molinuevo J, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. Plos One. 2014;9(2).

*4. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015;30(12):1600-09.

5. Wing YK, Lam SP, Zhang J, Leung E, Ho CL, Chen S, et al. Reduced striatal dopamine transmission in REM sleep behavior disorder comorbid with depression. Neurology. 2015;84(5):516-22.

6. Zoetmulder M, Nikolic M, Biernat H, Korbo L, Friberg L, Jennum P. Increased Motor Activity During REM Sleep Is Linked with Dopamine Function in Idiopathic REM Sleep Behavior Disorder and Parkinson Disease. J Clin Sleep Med. 2016;12(6):895-903.

7. Salsone M, Cerasa A, Arabia G, Morelli M, Gambardella A, Mumoli L, et al. Reduced thalamic volume in Parkinson disease with REM sleep behavior disorder: volumetric study. Parkinsonism Relat Disord. 2014;20(9):1004-8.

8. Arnaldi D, De Carli F, Picco A, Ferrara M, Accardo J, Bossert I, et al. Nigro-caudate dopaminergic deafferentation: a marker of REM sleep behavior disorder? Neurobiol Aging. 2015;36(12):3300-5.

9. Arnaldi D, Fama F, De Carli F, Morbelli S, Ferrara M, Picco A, et al. The role of the serotonergic system in REM sleep behavior disorder. Sleep. 2015;38(9):1505-9.
10. Arnaldi D, Morbelli S, Brugnolo A, Girtler N, Picco A, Ferrara M, et al. Functional neuroimaging and clinical features of drug naive patients with de novo Parkinson's disease and probable RBD. Parkinsonism Relat Disord. 2016;29:47-53.
11. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. Brain. 2000;123 (Pt 6):1155-60.
12. Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. Sleep. 2003;26(5):507-12.
13. Stiasny-Kolster K, Doerr Y, Moller JC, Hoffken H, Behr TM, Oertel WH, et al. Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. Brain. 2005;128(Pt 1):126-37.
14. Albin RL, Koeppe RA, Chervin RD, Consens FB, Wernette K, Frey KA, et al. Decreased striatal dopaminergic innervation in REM sleep behavior disorder. Neurology. 2000;55(9):1410-2.
15. Unger MM, Moller JC, Stiasny-Kolster K, Mankel K, Berg D, Walter U, et al. Assessment of idiopathic rapid-eye-movement sleep behavior disorder by transcranial sonography, olfactory function test, and FP-CIT-SPECT. Mov Disord. 2008;23(4):596-9.
16. Iranzo A, Lomena F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol. 2010;9(11):1070-7.

17. Kim YK, Yoon IY, Kim JM, Jeong SH, Kim KW, Shin YK, et al. The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. Eur J Neurol. 2010;17(3):487-92.

18. Iranzo A, Valldeoriola F, Lomena F, Molinuevo JL, Serradell M, Salamero M, et al. Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol. 2011;10(9):797-805.

19. Miyamoto M, Miyamoto T, Iwanami M, Muramatsu S, Asari S, Nakano I, et al. Preclinical substantia nigra dysfunction in rapid eye movement sleep behaviour disorder. Sleep Med. 2012;13(1):102-6.

*20. Iranzo A, Santamaria J, Valldeoriola F, Serradell M, Salamero M, Gaig C, et al. Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic REM sleep behavior disorder. Ann Neurol. 2017;82(3):419-28.

21. Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. Eur J Neurol. 2013;20(1):16-34.

22. De Marzi R, Seppi K, Hogl B, Muller C, Scherfler C, Stefani A, et al. Loss of dorsolateral nigral hyperintensity on 3.0 tesla susceptibility-weighted imaging in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol. 2016;79(6):1026-30.

23. Frosini D, Cosottini M, Donatelli G, Costagli M, Biagi L, Pacchetti C, et al. Seven tesla MRI of the substantia nigra in patients with rapid eye movement sleep behavior disorder. Parkinsonism Relat Disord. 2017;43:105-09.

24. Pyatigorskaya N, Gaurav R, Arnaldi D, Leu-Semenescu S, Yahia-Cherif L, Valabregue R, et al. Magnetic Resonance Imaging Biomarkers to Assess Substantia Nigra Damage in Idiopathic Rapid Eye Movement Sleep Behavior Disorder. Sleep. 2017;40(11).

*25. Li Y, Kang W, Yang Q, Zhang L, Zhang L, Dong F, et al. Predictive markers for early conversion of iRBD to neurodegenerative synucleinopathy diseases. Neurology. 2017;88(16):1493-500.

26. Varrone A, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Booij J, et al. European multicentre database of healthy controls for [123I]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.

27. Tossici-Bolt L, Dickson JC, Sera T, de Nijs R, Bagnara MC, Jonsson C, et al. Calibration of gamma camera systems for a multicentre European (1)(2)(3)I-FP-CIT SPECT normal database. Eur J Nucl Med Mol Imaging. 2011;38(8):1529-40.

28. Nobili F, Naseri M, De Carli F, Asenbaum S, Booij J, Darcourt J, et al. Automatic semi-quantification of [123I]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.

29. Buchert R, Kluge A, Tossici-Bolt L, Dickson J, Bronzel M, Lange C, et al. Reduction in camera-specific variability in [(123)I]FP-CIT SPECT outcome measures by image reconstruction optimized for multisite settings: impact on age-dependence of the specific binding ratio in the ENC-DAT database of healthy controls. Eur J Nucl Med Mol Imaging. 2016;43(7):1323-36.

30. Dickson JC, Tossici-Bolt L, Sera T, Booij J, Ziebell M, Morbelli S, et al. The impact of reconstruction and scanner characterisation on the diagnostic capability of a normal database for [(123)I]FP-CIT SPECT imaging. EJNMMI Res. 2017;7(1):10.

31. Tossici-Bolt L, Dickson JC, Sera T, Booij J, Asenbaun-Nan S, Bagnara MC, et al. [(123)I]FP-CIT ENC-DAT normal database: the impact of the reconstruction and quantification methods. EJNMMI Phys. 2017;4(1):8.

*32. Postuma RB, Iranzo A, Hogl B, Arnulf I, Ferini-Strambi L, Manni R, et al. Risk factors for neurodegeneration in idiopathic rapid eye movement sleep behavior disorder: a multicenter study. Ann Neurol. 2015;77(5):830-39.

33. Walker Z, Costa DC, Walker RWH, Shaw K, Gacinovic S, Stevens T, 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.