*Review*

# Lewy body dementia

L. BONANNI, R. FRANCIOTTI, M. RUSSO, C. CARRARINI, A. THOMAS, M. ONOFRJ

*Department of Neuroscience, Imaging and Clinical Sciences,*
*University "Gabriele d'Annunzio" of Chieti-Pescara, Italy*

***SUMMARY:*** *Dementia with Lewy bodies represents the second most common cause of neurodegenerative dementia after Alzheimer's disease. The Dementia with Lewy Bodies Consortium has refined its recommendations about the clinical and pathologic diagnosis of dementia with Lewy bodies, updating the previous report, which has been in widespread use for the last decade. The revised dementia with Lewy bodies consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers, and give guidance about optimal methods to establish and interpret these. Important new information has been updated about previously reported aspects of dementia with Lewy bodies, with increased diagnostic weighting given to REM sleep behavior disorder and $^{123}$iodine-metaiodobenzylguanidine myocardial scintigraphy. The diagnostic role of other neuroimaging, electrophysiological, and laboratory investigations is also better specified. Substantial progress has been made since the previous report in the detection and recognition of dementia with Lewy bodies as a common and important clinical disorder.*

***KEY WORDS:*** *Biomarkers, Consensus criteria, Dementia with Lewy bodies, EEG abnormalities, Magnetic resonance imaging studies, Treatment options.*

## OVERVIEW

Dementia with Lewy bodies is the second most common form of neurodegenerative dementia after Alzheimer's disease.

DLB tends to be underdiagnosed during life and mostly misdiagnosed as AD, due to clinical overlap between the two diseases.

It is important, however, to differentiate between these two forms of dementia since the earliest stages because, compared to patients with AD, those with DLB may be considerably more sensitive to adverse effects of neuroleptics[5] and may exhibit faster disease progression[45] and different response to ChEIs[30]. To reach a satisfactorily accuracy of the diagnosis of DLB, great emphasis has been placed on methods evaluating the uptake of either DAT in basal ganglia[44,52] or MIBG in the myocardium[54]. These methods, respectively exploring the integrity of the nigrostriatal dopaminergic system and of postganglionic sympathetic cardiac innervation, have been suggested to improve clinical diagnostic accuracy of DLB, but there is a clear need of other biomarkers to assist with accurate identification of this entity.

Cognitively, DLB patients can display marked deficits in executive and visuo-visuo/spatial-perceptual function, as well as marked variations in their level of arousal and attention, which are typically known as cognitive fluctuations[29,39,40,42]. Clinical features associated with DLB also include spontaneous motor

Correspondence: Prof. Laura Bonanni, SSD di Neurologia, Dipartimento di Neuroscienze, Imaging e Scienze Cliniche, via dei Vestini 31, 66100 Chieti (CH), Italy, tel. 085-34178; e-mail: laura.bonanni@unich.it.
Progress in Neuroscience 2019; 4 (1-4): 27-32.
*ISSN: 2240-5127*
doi: 10.14588/PiN.2019.Bonanni.27

***LIST OF ACRONYMS AND ABBREVIATIONS:*** **$^{123}$I-FP-CIT** = [$^{123}$I]-N-(3-FluoroPropyl)-2-Carbomethoxy-3-(4-Iodophenyl) norTropane; **AD** = Alzheimer's disease; **ChEIs** = CholinEsterase Inhibitors; **CIS** = Cingulate Island Sign; **DAT** = Dopamine Transporter; **DLB** = Dementia with Lewy bodies; **DTI** = Diffusion Tensor Imaging; **EEG** = ElectroEncephaloGram; **GM** = Grey Matter; **FDG-PET** = Fluoro-Dexosi-Glucose Positron Emission Tomography; **GM** = Gray Matter; **MIBG** = MetaIodoBenzylGuanidine; **MMSE** = Mini-Mental State Examination; **MRI** = Magnetic Resonance Imaging; **NAA/tCr** = N-Acetylaspartate/Total Creatine; **PSG** = PolySomnoGraphy; **RBD** = Rapid eye movement sleep Behavior Disorder; **REM** = Rapid Eye Movement; **tCho/tCr** = total Cholines/tCr = total creatines; **SPECT** = Single Photon Emission Computed Tomography.

features of parkinsonism[39], but it is the non-motor manifestations including visual hallucinations, autonomic dysfunction, syncope, repeated falls, REM sleep behaviour disorder, delusions and depression, to represent the most disruptive symptoms for patients and their caregivers[39].

There are also a number of treatment challenges. CHEIs may produce substantial reduction in apathy and improve visual hallucinations and delusions in DLB[40]. The use of antipsychotics for the acute management of substantial behavioral disturbance, delusions, or visual hallucinations comes with attendant mortality risks in patients with dementia, and particularly in the case of DLB they should be avoided whenever possible, given the increased risk of a serious sensitivity reaction[36,42]. Low-dose quetiapine may be relatively safer[34] than other antipsychotics and is widely used. There is a positive evidence base for clozapine in PD psychosis, but efficacy and tolerability in DLB have not been established. Newer drugs targeting the serotonergic system, such as pimavanserin[15], may be alternatives, but controlled clinical trial data in DLB are needed. Although depressive symptoms are common in DLB, trial data are insufficient.

DLB patients may benefit from levodopa preparations introduced at low doses and increased slowly to the minimum required to minimize motor disability without exacerbating psychiatric symptoms[25,41].

The Dementia with Lewy Bodies Consortium has refined its recommendations about the clinical and pathologic diagnosis of DLB. The revised DLB consensus criteria now distinguish clearly between clinical features and diagnostic biomarkers.

Important new information has been updated about previously reported aspects of DLB, with increased diagnostic weighting given to REM sleep behavior disorder. The diagnostic role of other neuroimaging, electrophysiological, and laboratory investigations is also better specified. Substantial progress has been made since the previous report in the detection and recognition of DLB as a common and important clinical disorder. During that period DLB has been incorporated as a separate nosological entity into DSM-5, as major neurocognitive disorder with Lewy bodies. 'There remains a pressing need to understand the underlying neurobiology and pathophysiology of DLB, to develop and deliver clinical trials with both symptomatic and disease-modifying agents, and to help patients and carers worldwide to inform themselves about the disease, its prognosis, best available treatments, ongoing research, and how to get adequate support'.

A collection of studies have been recently performed in order to define possible specific pathophysiological mechanisms underlying the appearance of specific clinical features of DLB, with the double aim to explain clinical presentation and potentially to provide possible diagnostic markers of disease[38].

In the present chapter we will summarize the main results of studies focused on DLB biomarkers and we will underline the significance of each of these biomarkers in terms of diagnostic accuracy and of pathophysiological mechanisms. Biomarkers will be divided in two sections, as suggested by the last Consensus document[38]: Indicative and supportive biomarkers. Major emphasis will be given to EEG and MRI studies which are the main fields of contributions by the authors.

## □ INDICATIVE BIOMARKERS

■ **SPECT-DAT SCAN.** The functional integrity of dopaminergic nigrostriatal pathway can be studied with SPECT imaging by using ligands of presynaptic DAT, such as $^{123}$I-FP-CIT. A reduction of SPECT ligand binding to DAT correlates with the loss of presynaptic dopamine. The rationale supporting the use of $^{123}$I-FP-CIT SPECT as a supportive tool in the diagnosis of DLB is represented by the pathological peculiarities of DLB, characterized by abnormal inclusion bodies (Lewy bodies) in limbic, neocortical and brainstem areas with concomitant nigrostriatal degeneration

and loss of pre-synaptic dopamine transporters in the striatum[37,53]. For these reasons, low dopamine transporter uptake in basal ganglia on $^{123}$I-FP-CIT SPECT has been listed as an indicative biomarker of DLB in the international consensus criteria for the diagnosis[38,55].

- **META-IODO-BENZYL-GUANIDINE.** Reduced uptake on metaiodobenzylguanidine myocardial scintigraphy. $^{123}$Iodine-MIBG myocardial scintigraphy quantifies postganglionic sympathetic cardiac innervation, which is reduced in DLB[43,51]. Useful sensitivity (69%) and specificity (87%) values for discriminating probable DLB from probable AD rise to 77% and 94% in milder cases (MMSE > 21). MIBG imaging was already described in the supportive feature section of the previous version of the Consortium on DLB Guidelines[39]. According to this report, delayed MIBG images resulted in highly reliable differentiation of DLB from AD with both the sensitivity and the specificity being 100%, regardless of the presence or absence of parkinsonism[55].
- **POLYSOMNOGRAPHY CONFIRMATION OF REM SLEEP WITHOUT ATONIA**. PSG demonstration of REM sleep without atonia[22,35] is a highly specific predictor of Lewy-related pathology. If the PSG shows REM sleep without atonia in a person with dementia and a history of RBD, there is a 90% likelihood of a synucleinopathy[7] sufficient to justify a probable DLB diagnosis even in the absence of any other core feature or biomarker. RBD is characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming[1,3,23,46,50]. RBD can occur without any coexisting neurological disorders or findings (so-called idiopathic RBD) and can be precipitated or aggravated by medications, such as selective serotonin or norepinephrine reuptake inhibitors[11,48]. All structural lesions associated with RBD identified to date have been localized in the dorsal midbrain, pons, or medulla.

## □ SUPPORTIVE BIOMARKERS

- **EEG.** Resting-state electroencephalographic rhythms have extensively been used as a possible tool to assess the neurophysiological correlates of dementia[12,13,24]. Quantitative EEG has demonstrated good discriminative capacity for DLB diagnosis as compared to AD with a predictive value of 100% in cohort studies, even at the stage of MCI[9,10] and the percentage of 90% in a multicentric cohort study[8]. Specifically, discriminant analysis detected specific cut-offs for every EEG mathematical descriptor; dominant frequency = 8, dominant frequency variability = 2.2 Hz, frequency prevalence pre-alpha = 33%, FP alpha = 41% for posterior derivations. The occipital low frequency alpha 2 source activity showed a classification accuracy of 75% in the contrast between the AD and DLB patients[4].
- **STRUCTURAL IMAGING STUDIES (PRESERVATION OF MEDIAL TEMPORAL GREY MATTER).** Recent advance in structural MRI allows to perform physical measurements of brain cortical thickness for each individual and to map, within and between groups, the macrostructural changes in GM regions. The measurement of the cortical thickness[21] showed 82% sensitivity and 85% specificity in differentiating AD from DLB[28]. At cortical level, DLB patients show a preservation of medial temporal GM as compared to AD[14,17,38] and a thinning in the posterior areas including the precuneus, superior parietal gyrus, cuneus, pericalcarine and lingual gyri[17]. Of note, the posterior atrophy of the cuneus, precuneus and superior parietal cortex has been related to visual deficit and hallucinations in DLB[6,17]. Moreover, increased rates of cortical thinning in the parietal regions were also correlated with motor deterioration in DLB[33].
- **FURTHER EVIDENCES COMING FROM STRUCTURAL IMAGING STUDIES.** At subcortical level, microstructural and macrostructural alterations have been also described in DLB patients. Macrostructural assessment highlighted that the hippocampus, especially in the cornu ammonis and subiculum, is relatively preserved in DLB as compared to AD[16,33]. Grey matter (GM) reduction was also observed in DLB patients in the adjacent extrahippocampal structures including the perirhinal and parahippocampal cortices(16). Microstructural damage of GM subcortical nuclei in DLB patients has been observed in the pons, hippocampus and thalamus[18,19,32]. Additionally, by combining structural MRI and DTI data, the thalamus was further divided in sub-regions according to their structural connectivity to cortex. The assessment of microstructural changes in each thalamic sub-region in DLB have revealed: microstructural grey matter preservation of the sub-regions which projects to temporal cortex[19],

alterations within the thalamic portions projecting to the prefrontal and parieto-occipital cortices and amydala[19]. Moreover, DLB patients present reduced structural connectivity within the anterior thalamic radiation, which projects to frontal cortex[48]. These results are in agreement with the role of thalamus in shaping the cortico-cortical control[49] and with emerging hypotheses suggesting that thalamic dysregulation could induce reduced levels of arousal and consciousness state[2]. In this context, we observed reduction of NAA/tCr (marker of axonal density) and increase of tCho/tCr (marker of cholinergic dysfunction) in DLB patients, which correlated with frequency and severity of fluctuating cognition in DLB[18]. Moreover, it was observed that the microstructural damage of the thalamic portions projecting to cortical posterior regions including parietal and occipital lobes is closely related to the presence and severity of visual hallucinations[19]. These findings are in agreement with the role of the pulvinar in the visual processing[47] and with recent reports from neuropathological studies showing severe neuronal loss in the medial pulvinar in post-mortem brain tissue acquired from patients with DLB[20].

- **Cingulate island sign.** The CIS, a term referring to sparing of the posterior cingulate relative to the precuneus and cuneus, has been proposed as an FDG-PET imaging feature of DLB[27,31] due to its good diagnostic power to distinguish DLB patients from AD. The preservation of the CIS is not associated with Aβ load but does predict lower Braak neurofibrillary tangle stage in clinically diagnosed DLB cases[26]. Furthermore clinical symptoms of DLB (parkinsonism and global cognitive function) were found to be correlated with precuneus plus cuneus hypometabolism but not the CIS[26].

## REFERENCES


1. Abbott RD, Ross GW, White LR, Tanner CM, Masaki KH, Nelson JS et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology 2005; 65 (9): 1442-1446.
2. Akeju O, Loggia ML, Catana C, Pavone KJ, Vazquez R, Rhee J et al. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. eLife 2014; 3: e04499.
3. Arnulf I. Excessive daytime sleepiness in parkinsonism. Sleep Med Rev 2005; 9 (3): 185-200.
4. Babiloni C, Del Percio C, Lizio R, Noce G, Cordone S, Lopez S et al. Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study. Neurobiol Aging 2017; 55: 143-158.
5. Ballard CG, Holmes C, McKeith IG, O'Brien JT, Ince PG, Perry RH. Clinical symptoms in dementia with Lewy bodies: A prospective clinical and neuropathological comparative study with Alzheimer's disease. Neurology 1998; 50 (4): A183-A.
6. Blanc F, Colloby SJ, Cretin B, de Sousa PL, Demuynck C, O'Brien JT et al. Grey matter atrophy in prodromal stage of dementia with Lewy bodies and Alzheimer's disease. Alzheimers Res Ther 2016; 8: 31.
7. Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013; 14 (8): 754-762.
8. Bonanni L, Franciotti R, Nobili F, Kramberger MG, Taylor JP, Garcia-Ptacek S et al. EEG markers of dementia with Lewy bodies: a multicenter cohort Study. J Alzheimers Dis 2016; 54 (4): 1649-1657.
9. Bonanni L, Perfetti B, Bifolchetti S, Taylor JP, Franciotti R, Parnetti L et al. Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol Aging 2015; 36 (1): 434-445.
10. Bonanni L, Thomas A, Tiraboschi P, Perfetti B, Varanese S, Onofrj M. EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain 2008; 131 (Pt 3): 690-705.
11. Breen DP, Williams-Gray CH, Mason SL, Foltynie T, Barker RA. Excessive daytime sleepiness and its risk factors in incident Parkinson's disease. J Neurol Neurosurg Psychiatry 2013; 84 (2): 233-234.
12. Breslau J, Starr A, Sicotte N, Higa J, Buchsbaum MS. Topographic EEG changes with normal aging and SDAT. Electroencephalogr Clin Neurophysiol 1989; 72 (4): 281-289.
13. Briel RC, McKeith IG, Barker WA, Hewitt Y, Perry RH, Ince PG et al. EEG findings in dementia with Lewy bodies and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1999; 66 (3): 401-403.
14. Colloby SJ, Cromarty RA, Peraza LR, Johnsen K, Johannesson G, Bonanni L et al. Multimodal EEG-MRI in the differential diagnosis of Alzheimer's disease and dementia with Lewy bodies. J Psychiatr Res 2016; 78: 48-55.
15. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 2014; 383 (9916): 533-540.

16. Delli Pizzi S, Franciotti R, Bubbico G, Thomas A, Onofrj M, Bonanni L. Atrophy of hippocampal subfields and adjacent extrahippocampal structures in dementia with Lewy bodies and Alzheimer's disease. Neurobiol Aging 2016; 40: 103-109.

17. Delli Pizzi S, Franciotti R, Tartaro A, Caulo M, Thomas A, Onofrj M et al. Structural alteration of the dorsal visual network in DLB patients with visual hallucinations: a cortical thickness MRI study. PLoS One 2014; 9 (1): e86624.

18. Delli Pizzi S, Franciotti R, Taylor JP, Thomas A, Tartaro A, Onofrj M et al. Thalamic involvement in fluctuating cognition in dementia with Lewy bodies: magnetic resonance evidences. Cereb Cortex 2015; 25 (10): 3682-3689.

19. Delli Pizzi S, Maruotti V, Taylor JP, Franciotti R, Caulo M, Tartaro A et al. Relevance of subcortical visual pathways disruption to visual symptoms in dementia with Lewy bodies. Cortex 2014; 59: 12-21.

20. Erskine D, Taylor JP, Firbank MJ, Patterson L, Onofrj M, O'Brien JT et al. Changes to the lateral geniculate nucleus in Alzheimer's disease but not dementia with Lewy bodies. Neuropathol Appl Neurobiol 2016; 42 (4): 366-376.

21. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000; 97 (20): 11050-11055.

22. Frauscher B, Iranzo A, Gaig C, Gschliesser V, Guaita M, Raffelseder V et al. Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. Sleep 2012; 35 (6): 835-847.

23. Gao J, Huang X, Park Y, Hollenbeck A, Blair A, Schatzkin A et al. Daytime napping, nighttime sleeping, and Parkinson disease. Am J Epidemiol 2011; 173 (9): 1032-1038.

24. Giaquinto S, Nolfe G. The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroencephalogr Clin Neurophysiol 1986; 63 (6): 540-546.

25. Goldman JG, Goetz CG, Brandabur M, Sanfilippo M, Stebbins GT. Effects of dopaminergic medications on psychosis and motor function in dementia with Lewy bodies. Mov Disord 2008; 23 (15): 2248-2250.

26. Graff-Radford J, Murray ME, Lowe VJ, Boeve BF, Ferman TJ, Przybelski SA et al. Dementia with Lewy bodies: basis of cingulate island sign. Neurology 2014; 83 (9): 801-809.

27. Imamura T, Ishii K, Sasaki M, Kitagaki H, Yamaji S, Hirono N et al. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease: a comparative study using positron emission tomography. Neurosci Lett 1997; 235 (1-2): 49-52.

28. Lebedev AV, Westman E, Beyer MK, Kramberger MG, Aguilar C, Pirtosek Z et al. Multivariate classification of patients with Alzheimer's and dementia with Lewy bodies using high-dimensional cortical thickness measurements: an MRI surface-based morphometric study. J Neurol 2013; 260 (4): 1104-1115.

29. Lee DR, Taylor JP, Thomas AJ. Assessment of cognitive fluctuation in dementia: a systematic review of the literature. Int J Geriatr Psychiatry 2012; 27(10): 989-998.

30. Levy R. Alzheimer's disease and Lewy body dementia. Br J Psychiatry 1994; 164(2): 268.

31. Lim SM, Katsifis A, Villemagne VL, Best R, Jones G, Saling M et al. The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. J Nucl Med 2009; 50 (10): 1638-1645.

32. Mak E, Su L, Williams GB, O'Brien JT: Neuroimaging characteristics of dementia with Lewy bodies. Alzheimers Res Ther 2014; 6 (2): 18.

33. Mak E, Su L, Williams GB, Watson R, Firbank M, Blamire A et al. Differential atrophy of hippocampal subfields: a comparative study of dementia with Lewy bodies and Alzheimer sisease. Am J Geriatr Psychiatry 2016; 24 (2): 136-143.

34. Maust DT, Schneider LS, Kales HC. Estimating mortality associated with antipsychotics and other psychotropics - Reply. JAMA Psychiatry 2015; 72 (10): 1058.

35. McCarter SJ, St Louis EK, Duwell EJ, Timm PC, Sandness DJ, Boeve BF et al. Diagnostic thresholds for quantitative REM sleep phasic burst duration, phasic and tonic muscle activity, and REM atonia index in REM sleep behavior disorder with and without comorbid obstructive sleep apnea. Sleep 2014; 37 (10):1649-1662.

36. McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. BMJ 1992; 305 (6855): 673-678.

37. McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J et al. Dementia with Lewy bodies. Lancet Neurol 2004; 3 (1): 19-28.

38. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017; 89 (1): 88-100.

39. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005; 65 (12): 1863-1872.

40. Mollenhauer B, Forstl H, Deuschl G, Storch A, Oertel W, Trenkwalder C. Lewy body and parkinsonian dementia: common, but often misdiagnosed conditions. Dtsch Arztebl Int 2010; 107 (39): 684-691.

41. Molloy S, McKeith IG, O'Brien JT, Burn DJ. The role of levodopa in the management of dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2005; 76 (9): 1200-1203.

42. Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology 2004; 63 (11): 2091-2096.

43. Nakajima K, Okuda K, Yoshimura M, Matsuo S, Wakabayashi H, Imanishi Y et al. Multicenter cross-calibration of I-123 metaiodobenzylguanidine heart-to-mediastinum ratios to overcome camera-collimator variations. J Nucl Cardiol 2014; 21 (5): 970-978.
44. O'Brien JT, Colloby S, Fenwick J, Williams ED, Firbank M, Burn D et al. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with Lewy bodies. Arch Neurol 2004; 61 (6): 919-925.
45. Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, Katzman R et al. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. Neurology 1998; 51 (2): 351-357.
46. Ratti PL, Negre-Pages L, Perez-Lloret S, Manni R, Damier P, Tison F et al. Subjective sleep dysfunction and insomnia symptoms in Parkinson's disease: Insights from a cross-sectional evaluation of the French CoPark cohort. Parkinsonism Relat Disord 2015; 21 (11): 1323-1329.
47. Saalmann YB, Pinsk MA, Wang L, Li X, Kastner S. The pulvinar regulates information transmission between cortical areas based on attention demands. Science 2012; 337 (6095): 753-756.
48. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol 2015; 14(1): 57-64.
49. Sherman SM. The thalamus is more than just a relay. Curr Opin Neurobiol 2007; 17(4): 417-422.
50. Simuni T, Caspell-Garcia C, Coffey C, Chahine LM, Lasch S, Oertel WH et al. Correlates of excessive daytime sleepiness in de novo Parkinson's disease: A case control study. Mov Disord 2015; 30 (10): 1371-1381.
51. Treglia G, Cason E. Diagnostic performance of myocardial innervation imaging using MIBG scintigraphy in differential diagnosis between dementia with lewy bodies and other dementias: a systematic review and a meta-analysis. J Neuroimaging 2012; 22 (2): 111-117.
52. Walker Z, Costa DC, Walker RW, 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): 134-140.
53. Weisman D, McKeith I. Dementia with Lewy bodies. Semin Neurol 2007; 27 (1): 42-47.
54. Yoshita M, Taki J, Yamada M. A clinical role for [(123)I]MIBG myocardial scintigraphy in the distinction between dementia of the Alzheimer's-type and dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2001; 71 (5): 583-588.
55. Yoshita M, Taki J, Yokoyama K, Noguchi-Shinohara M, Matsumoto Y, Nakajima K et al. Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. Neurology 2006; 66 (12): 1850-1854.

***Disclosure.*** *The Author declare no conflicts of interest.*