How to Distinguish Dementia with Lewy Bodies from Alzheimer Disease?

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Abstract: Dementia with Lewy (DLB) bodies is the most common type of degenerative dementia after Alzheimer Disease (AD). Although an accurate diagnosis of DLB is important for adequate prognosis and therapy, its differentiation from other dementias and, especially, from AD may be extremely challenging for clinicians, as highlighted by the high variability in reported sensitivity (0.22 – 0.83) and specificity (0.79 – 1.00) rates for a diagnosis of probable DLB applying current clinical criteria. Various kinds of imaging procedures, including conventional MRI and brain perfusion SPECT, have been proposed for improving diagnostic accuracy, especially for most controversial cases. Among such techiques, those using radioactive tracers measuring the striatal binding at pre-synaptic dopamine transporter sites or myocardial uptake in post-ganglionic sympathetic fibers have emerged as the most useful for diagnostic purposes.

Keywords: Alzheimer disease, Dementia with Lewy bodies, DAT scan, MIBG myocardial scintigraphy.

DEMENTIA WITH LEWY BODIES: CLINICAL PHENOMENOLOGY AND DIAGNOSTIC CONTROVERSIES

Dementia with Lewy bodies (DLB) has been reported to be the second most common form of degenerative dementia, after Alzheimer Disease (AD). The importance of identifying this entity lies essentially in its pharmacologic management, with a potential good response to cholinesterase inhibitors [1], but increased sensitivity to adverse effects of neuroleptic drugs [2, 3].

Much attention has been focused on the identification of reliable criteria that may help the clinician to discriminate DLB from other dementias, and especially from AD [4]. In addition to cognitive decline, the core clinical features of DLB, according to the Consortium on DLB criteria [4, 5], are visual hallucinations (VH), which typically are recurrent, well formed and detailed, fluctuating cognition with pronounced variations in attention and alertness, and spontaneous (i.e., not drug-induced) features of parkinsonism, with an overrepresentation of the "postural instability-gait difficulty" phenotype [6]. The motor manifestations of parkinsonism may also include limb rigidity, bradykinesia, and a symmetrical postural tremor, while unilateral rest tremor is relatively uncommon. Neuropsychologically, compared to AD, patients with DLB tend to show a different pattern of cognitive impairment, with more preserved memory [7], but worse performances on attentional and executive tasks [8, 9] and on tests of visuospatial/constructional abilities [10, 11]. However, despite emphasis placed on these distinctive characteristics, while neuropathologic series have demonstrated high accuracy for the clinical diagnosis of AD [12], the accuracy for the clinical diagnosis of DLB using the criteria originally suggested by the Consortium on DLB [4] has been in general less satisfactory [13-17], essentially because some of the "core" clinical features of DLB may not invariably appear even during the entire course of the disease [18] or may overlap with some extent with AD [19]. The presence and severity of concurrent AD pathology in DLB modifies the clinical presentation, with decreased rates of VH and parkinsonism as neurofibrillary tangle pathology increases, making these cases harder to be recognized [19]. Another reason for "missing" DLB clinically, which clearly emerged from the above mentioned studies [13-17], was the authors' failure to reliably identify fluctuations, a symptom which even today remains hard to define, identify, and reliably assess, despite recent proposals of structured methods for its detection [20, 21]. As a result, using Consensus clinical criteria as originally formulated [4], DLB often goes unrecognized and mostly misdiagnosed as AD.

To obviate this, diagnostic criteria for DLB have recently been updated [5] and, although it was still acknowledged the importance of VH, fluctuations in attention and vigilance, and spontaneous parkinsonism as "core" features of the disease, a substantial weight has also been given to REM behaviour disorder (RBD), neuroleptic hypersensitivity, and decreased striatal binding at pre-synaptic dopamine transporter sites [22-24], so that the presence of at least one of these features with just one "core" symptom/sign is now considered sufficient to warrant a diagnosis of probable DLB. It should be highlighted, however, that at least two of the "suggestive" features (neuroleptic hypersensitivity and decreased striatal binding of radioactive tracers) would not be useful to corroborate a hypothetical diagnosis of DLB (shift from the possible to the probable category) if parkinsonism is the only "core" feature exhibited by the patient. In this case, in fact, reduced striatal binding and

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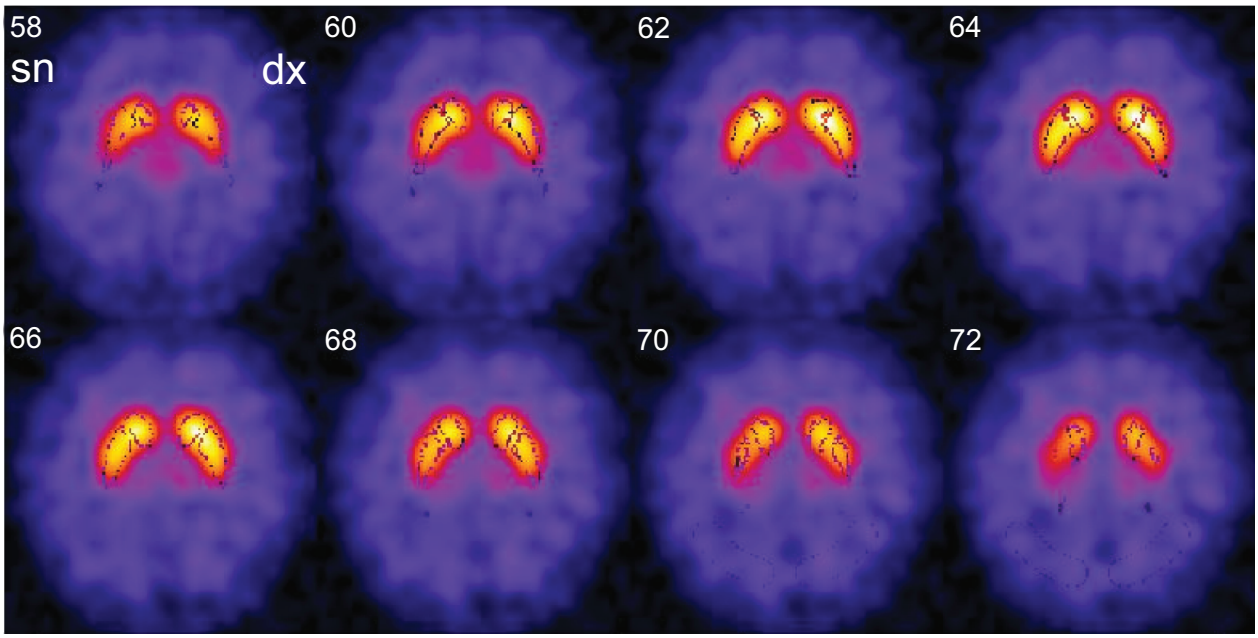
exacerbation of motor signs following antipsychotic treatment are largely expected (circularity). It is also worth mentioning that, although decreased striatal binding of radioactive tracers has been proven to have good sensitivity and specificity to DLB [22-24], and severe nigrostriatal degeneration, as indicated by abnormal (low binding) dopamine transporter activity on SPECT or PET imaging, is considered the most reliable biological diagnostic marker for this condition, there are clinical and pathologic studies [25, 26] where this finding has also been reported for patients with AD. Fig. (**1**) shows examples of a normal dopamine transporter scan (**a**) and of a patient affected with DLB (**b**).

For these reasons, alternative methods to support the diagnosis of DLB have been proposed, such as myocardial scintigraphy with metaiodobenzyl guanidine (MIBG), an analogue of norepinephrine whose decreased uptake reflects the damage of post-ganglionic sympathetic cardiac innervation [27-29]. It is well known that severe autonomic dysfunction causes many symptoms, including orthostatic hypotension, that is more frequently seen in synucleinopathies [multiple system atrophy (MSA) > DLB > idiopathic Parkinson disease (PD)] than in AD or frontotemporal dementias. MIBG uptake has been found to be particularly decreased in DLB patients with orthostatic

(**a**)



(**b**)

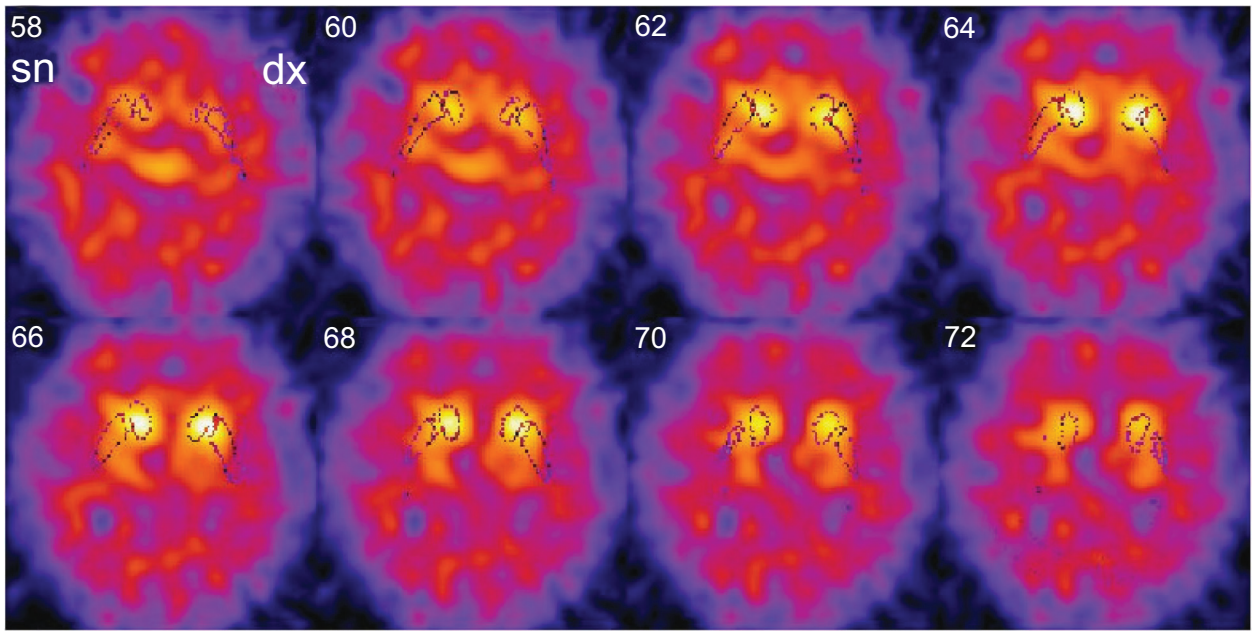


Fig. (1). Transverse reconstruction ^{123}I-FPCIT SPECT scan in Alzheimer dementia (**a**) and in Lewy body dementia (**b**). Black dots are automatically drawn according to software BasGan [52].

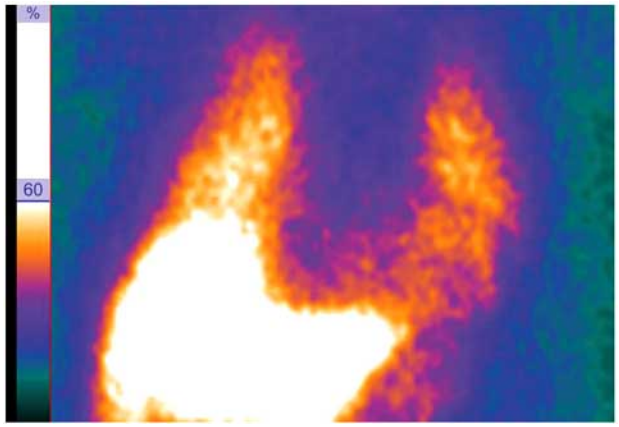
hypotension [30]. However, as a reduction in tracer binding at pre-synaptic dopamine transporter sites may reflect a level of nigrostriatal degeneration still insufficient to determine clinical parkinsonism, so reduced myocardial MIBG uptake may reflect pathologic changes in post-ganglionic sympathetic cardiac innervation still insufficient to determine orthostatic hypotension. Therefore, for the high sensitivity to pathologic changes caused by DLB (the presence of Lewy neurites has been described in the cardiac plexus and in post-ganglionic sympathetic cardiac terminals) even before clinical expression, MIBG scintigraphy could indeed overcome the difficulties of clinical criteria alone to identify cases with DLB. Decreased MIBG uptake on myocardial scintigraphy has also been reported to have excellent specificity to DLB (and PD). A normal uptake is, in fact, expected, in MSA (where structural changes in the autonomic system are essentially restricted to pre-ganglionic sympathetic innervation), in AD (where autonomic dysfunction is rare and, when present, is generally attributed to structural changes in the brainstem and/or hypothalamus) [31], and in frontotemporal dementia [32]. MIBG scintigraphy (examples in Fig. **2a**, **b**) may be preferred to dopamine transporter (DAT) imaging because it is considerably less expensive and its sensitivity and specificity to DLB is completely independent of the presence of parkinsonism [31]. On the other hand, compared to DAT-imaging, MIBG scintigraphy has some disadvantages, such as the fact that several common illnesses in the elderly (including heart infarct, heart failure, dilatative cardiomyopathy, and dysautonomic diabetic neuropathy) may interfere with MIBG uptake. This can lead to false positive results in patients suffering from dementias other than DLB. In this respect, it should be highlighted that the complete (100%) sensitivity and specificity of MIBG scintigraphy to DLB recently reported by some investigators [31] has been obtained in a highly selected sample, because all patients with medical conditions potentially interfering with MIBG uptake were excluded from the study.

Another issue is the lack of standardization with regard to timing, acquisition, and processing of images. Although planar acquisitions are used by all investigators [27-37], acquisition times after MIBG injection are extremely variable (ranging from 15 to 120 minutes for early images and 200 to 240 minutes for delayed images) and heart-to-mediastinum ratios are determined on regions of interest that differ in shape and size, explaining the cut-off variability reported in the literature (1.5-2.6 for late images) [27-37].

Other Laboratory and Neuroimaging Investigations

In DLB, the standard EEG may show early slowing, epoch-by-epoch fluctuation, and transient slow-wave activity [38]. EEG variability, assessed by mean frequency analysis and compressed spectral arrays (CSA), may be particularly useful in discriminating between DLB from AD since the earliest stages of dementia. Specifically, particular frequency bands (5.6-7.9Hz) seem to be peculiar to DLB and appear to be related to the presence and severity of cognitive fluctuations [39]. As of yet, there are no clinically applicable genotypic or CSF markers to support a diagnosis of DLB, although phosphorilated and total tau are in general lower in DLB than AD [40, 41]. Conversely, Abeta 42 is usually comparable, reflecting high plaque deposition in both DLB and AD [42]. On coronal MRI, hippocampal and medial temporal lobe atrophy is less pronounced in DLB than AD [43]. This is in keeping with autopsy findings but, in early-stage dementia, preservation of medial temporal lobe volumes may be seen in both diseases. Occipital hypoperfusion/hypometabolism on SPECT [44] or PET [45] are changes usually associated to DLB, but not to AD. However, these abnormalities are seen in only approximately 50-70% of DLB cases (high specificity, but somewhat poor sensitivity). Of note, in two recent studies comparing brain perfusion SPECT and MIBG myocardial scintigraphy, the latter was significantly superior in the identification of DLB subjects [46, 47].

(**a**)



(**b**)

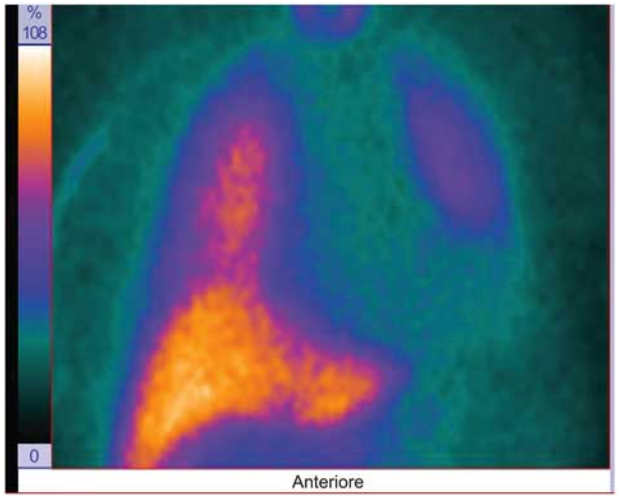


Fig. (2). Planar scintigraphy with ^{123}I-MIBG in Alzheimer dementia (**a**) and in Lewy body dementia (**b**).

CONCLUSION

DLB may present as a primary neuropsychiatric syndrome characterized by cognitive decline, in which case diagnostic differentiation is from other causes of dementia, particularly AD, or it may develop later, in a patient already labelled as having PD. The latter presentation poses considerably less challenge to the clinician's diagnostic

ability since, in AD, extrapyramidal signs (EPS) are variable and, if present, usually follow the onset of cognitive deterioration. Such an order of presentation of cognitive and motor features is also typical of DLB, making its distinction from AD with extrapyramidal signs extremely hard.

There is evidence that the three core features of DLB (VH, fluctuations, and parkinsonism) do not have the same diagnostic weight. For example, in a recent neuropathologic series of patients with mild dementia [48], while VH at presentation were a strong predictor of DLB at autopsy, the presence of parkinsonism did not appear to enhance diagnostic accuracy. In fact, EPS were exhibited by only approximately one fourth of the DLB cases and, above all, there were no significant differences in its prevalence between the cases with DLB and those with AD (26% *vs* 16%). An important implication of this study is that, in early-stage dementia, several patients clinically labeled as DLB on the basis of the presence of parkinsonism alone have a high risk to be misdiagnosed (false positivity). It is especially in these cases (labeled as possible DLB on the basis of the presence of a single core feature) that ancillary investigations, such as neuroimaging, might be most important in enhancing accuracy of diagnosis.

With one exception [49], clinical-pathologic correlations with the original DLB criteria [4] have not been very good [13-17]. Specifically, most of validation studies [13-17] have shown good specificity, but only modest sensitivity, for the clinical diagnosis of probable DLB. That is, applying the Consensus criteria as originally formulated, the presence of two or more core features (clinically, probable DLB) was strongly predictive of DLB at autopsy but, unfortunately, few patients with DLB at autopsy showed more than one core feature during the entire course of the disease. As a result, DLB was underestimated and mostly misdiagnosed as AD. It is likely that the new criteria [5] might improve this situation. In support of this, is a recent validation study [50] which, using the revised criteria and placing particular emphasis on RBD, has shown not only excellent specificity, but also high sensitivity (87%) for the diagnosis of probable DLB. There is also preliminary evidence of the potentially important role of ancillary investigations in improving diagnostic accuracy in diagnostically uncertain cases, as indicated by a recent study of patients with only possible DLB, where an abnormal DAT-scan at baseline strongly predicted the appropriateness of this diagnosis, preceding the appearance of other distinctive clinical features [51].

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