

# NON-AD DEMENTIAS: ALPHA-SYNUCLEINOPATHIES

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## Overview

With the advent of  $\alpha$ -synuclein immunocytochemistry, some of the “Parkinson-plus” syndromes have been reclassified, resulting in the major  $\alpha$ -synucleinopathies being Lewy body disease (LBD) and multiple system atrophy (MSA). LBD can manifest clinically as a dementia-predominant syndrome with concurrent or subsequent parkinsonism (ie, dementia with Lewy bodies or DLB), a motor-predominant syndrome with subsequent dementia (Parkinson’s disease with dementia or PDD), or an autonomic-predominant syndrome (pure autonomic failure or PAF). The term MSA is applied to both the clinical syndrome and the pathologically-defined disease. Since clinically-significant cognitive impairment is uncommon in MSA, and DLB and PDD are so complex, this segment of the course will focus on DLB and PDD. Readers are also encouraged to review recent papers on these disorders.<sup>1, 2</sup>

## Dementia with Lewy Bodies

### *Clinical features*

The criteria for the clinical diagnosis of DLB as per the Consortium on Dementia with Lewy Bodies (CDLB or “McKeith criteria”), originally published in 1996<sup>3</sup>, were refined in 1999<sup>4</sup>. Further refinements to the criteria were suggested in 2005 as part of the Third Report of the DLB Consortium, and most recently in 2015 as part of the Fourth Report of the DLB Consortium. The criteria for the clinical diagnosis of DLB based on the Third Report of the DLB Consortium<sup>5</sup> are shown in **Table 1** (at the time of the writing of this syllabus, the proceedings from the Fourth Report had not yet been published). Attempts continue to be made to operationalize criteria for fluctuations, and better characterize the cognitive, visual hallucinations, parkinsonism, sleep, and autonomic aspects of DLB. The three core features are emphasized – recurrent fully formed visual hallucinations, fluctuations in cognition and/or arousal, and spontaneous parkinsonism,<sup>5</sup> and REM sleep behavior disorder (RBD) will soon be elevated as a fourth core feature. The clinical features of mild cognitive impairment (MCI) associated with Lewy body disease have been characterized, and as one would expect, impairment in the domains of attention/executive functioning and visuospatial functions, and presence of RBD, are the distinctive features.<sup>6</sup> The presence of RBD has recently been confirmed in a large autopsy series as the most reliable feature for diagnosing DLB in the setting of dementia.<sup>7</sup>

### *Neuropsychological features*

Neuropsychological testing typically shows impairment on measures of attention/concentration and visuospatial functioning in DLB, with performance on delayed recall measures being more variable and sometimes entirely normal.<sup>8-12</sup> A similar pattern of deficits—impaired visual perceptual-organizational skills, constructional praxis, and verbal fluency—have been demonstrated in patients with dementia plus RBD.<sup>13</sup> In a subsequent analysis in which the pattern of neuropsychological impairment was compared between one group of RBD/dementia patients and the other group of autopsy-proven AD patients, a double dissociation was identified, in which the RBD/dementia group had worse impairment on measures of attention, visual perceptual-organization, and letter fluency, while the AD group had significantly worse performance on confrontation naming and verbal memory.<sup>14</sup> This same pattern was then found in a group of patients with dementia and RBD but did not have parkinsonism or visual hallucinations.<sup>15</sup> These findings suggest that in the absence of visual hallucinations or parkinsonism, the presentation of dementia and RBD may indicate underlying LBD. These studies strongly support the role of neuropsychological testing, and the determination of whether RBD is present or not,<sup>16-18</sup> in the differential diagnosis of patients with dementia.

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**Table 1. Criteria for the clinical diagnosis of dementia with Lewy bodies: Third Report of the DLB Consortium**

1. Central feature

- Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function and visuospatial ability may be especially prominent.

2. Core features (*two core features essential for a diagnosis of probable, one for possible DLB*)

- Fluctuating cognition with pronounced variations in attention and alertness
- Recurrent visual hallucinations that are typically well formed and detailed
- Spontaneous features of parkinsonism

3. Suggestive features (*one or more present in addition to one or more core features is sufficient for a diagnosis of probable DLB, and in the absence of any core features is sufficient for possible DLB*)

- REM sleep behaviour disorder (which may precede onset of dementia by several years)
- Severe neuroleptic sensitivity
- Abnormal (low uptake) in basal ganglia on SPECT dopamine transporter scan

4. Supportive features (*commonly present but lacking diagnostic specificity*)

- Repeated falls and syncope
- Transient, unexplained loss of consciousness
- Severe autonomic dysfunction which may occur early in disease e.g. orthostatic hypotension, urinary incontinence
- Systematized delusions
- Hallucinations in other modalities
- Depression
- Relative preservation of medial temporal lobe structures on CT/MRI scan
- Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
- Prominent slow wave activity on EEG with temporal lobe transient sharp waves

A diagnosis of DLB is less likely in the presence of:

Cerebrovascular disease evident as focal neurological signs or on brain imaging, or any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture.

From reference<sup>5</sup>

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*Neuroimaging features*

Hippocampal atrophy is well-established in patients with mild cognitive impairment (MCI) and AD.<sup>19-21</sup> and DLB patients appear to have less hippocampal atrophy on CT and MRI scans compared to AD and vascular dementia.<sup>22-24</sup> Hence, the finding of no significant hippocampal atrophy in a patient with mild to moderate dementia may suggest that the underlying histopathology is more likely to be LBD than AD. Functional neuroimaging studies have tended to show abnormalities in parieto-occipital cortices.<sup>25, 26</sup> The so-called “posterior cingulate island sign,” in which the posterior cingulate metabolism is relatively preserved and appears like an “island” surrounded by hypometabolic tissue, is a relatively consistent finding in DLB patients.<sup>27</sup> It should be noted that clinical experience using FDG-PET scans in patients with typical DLB features is variable, and one should not base a diagnosis of DLB primarily on the FDG-PET findings. Dopamine transporter imaging using ioflupane SPECT is now available in many countries – studies in Europe have shown that reduced dopamine transporter uptake in the basal ganglia in those with dementia is highly suggestive of underlying LBD.<sup>28</sup> RBD is often present in DLB and this may be a particularly specific feature in the setting of dementia.<sup>7, 13, 29-31</sup> Early reports on DLB suggested that the disease course was more rapid than in AD, and the duration of symptoms in the case

described above was indeed rapid. Yet recent survival analyses indicate that the mean duration of symptoms between DLB and AD are similar.<sup>32</sup>

### *Neuropathologic features*

The recommendations from the Third Report of the DLB Consortium are to use  $\alpha$ -synuclein immunohistochemistry and a semi-quantitative grading of lesion density. The grading involves categorizing LB density into mild, moderate, severe and very severe, and then assessing the regional pattern of Lewy-related pathology by grading it using a template similar to that used in the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) for neuritic plaques. The likelihood that the neuropathologic findings is associated with a DLB clinical syndrome is determined, taking account both Alzheimer and Lewy body type pathology.<sup>5</sup> This scheme has undergone prospective clinicopathologic validation, with the results showing reasonably good performance, thereby suggesting that this scheme is useful for estimating the likelihood of the premortem DLB syndrome.<sup>33</sup> Relatively minor changes to the neuropathologic characterization of DLB are anticipated for the Fourth Report of the DLB Consortium.

### *Management*

No therapy has yet been identified that significantly alters  $\alpha$ -synuclein pathophysiology which is presumed to be central to Lewy body disease. The following approach addresses strategies for the five categories of symptomatology: cognitive impairment, neuropsychiatric features, motor dysfunction, sleep disorders, and autonomic dysfunction.<sup>34-36</sup>

*Cognitive impairment.* The cholinergic deficit in DLB is now well established, and the cholinesterase inhibitors have been shown in open-label and double-blind, placebo-controlled studies to modestly improve cognition and functional abilities (reviewed in detail in reference<sup>37</sup>). Despite the concern that cholinergic stimulation might worsen parkinsonism, this has not been a serious problem based on clinical experience and controlled studies.<sup>38</sup> Although federal approval is still lacking in most countries, most clinicians prescribe one of the cholinesterase inhibitors for DLB patients who do not have a contraindication to its use. Open label studies and clinical experience suggests that memantine provides more modest benefit for DLB patients, although a double-blind placebo-controlled trial did demonstrate efficacy and good tolerability.<sup>39</sup> Psychostimulants, carbidopa/levodopa, and the dopamine agonists can theoretically improve cognition, apathy, and psychomotor slowing, but controlled studies are only now being tested for efficacy.

*Neuropsychiatric features.* The presence of visual hallucinations is one of the most frequent and pervasive features of DLB, yet they do not require drug therapy if the hallucinations are not frightening. When fright occurs, or when paranoia develops with hallucinations, drug therapy is often necessary. Conventional neuroleptics which have been classically used to manage hallucinations can cause striking and irreversible parkinsonism—a phenomenon termed “neuroleptic sensitivity.” These agents are now strongly discouraged in the management of DLB,<sup>40</sup> underscoring the importance of accurate diagnosis in this condition. The cholinesterase inhibitors have been shown to improve hallucinations as well as apathy.<sup>38, 41-43</sup> There are reports of neuroleptic sensitivity even among the newer atypical neuroleptic agents, and some of these have been minimally effective for psychotic features.<sup>44</sup> The following agents have been reported to improve hallucinations, delusions, or agitation: clozapine<sup>45-47</sup>, risperidone<sup>48, 49</sup>, olanzapine<sup>50, 51</sup>, quetiapine<sup>47, 52</sup>, as well as the cholinesterase inhibitors. Therefore, if problematic hallucinations, delusions, or agitation occurs in patients with DLB who do not respond to the cholinesterase inhibitors, clinicians often consider quetiapine, clozapine, or olanzapine. There is insufficient evidence on the efficacy of ziprasidone and aripiprazole. Pimavanserin was recently approved in several countries for the management of hallucinations and delusions associated with Parkinson's disease psychosis<sup>53</sup>, no trial data using this agent in DLB is available yet. Orthostatism can occur with any of the atypical neuroleptic agents. Valproic acid and carbamazepine have mood-stabilizing properties and may be appropriate for some patients.

No controlled trials using SSRIs or SNRIs have been conducted in DLB. The SSRIs are usually effective and well-tolerated for managing depression. Due to the anticholinergic properties of the tricyclic antidepressants, these agents should generally be avoided in DLB. Electroconvulsive therapy (ECT) can be effective in some patients without significantly worsening cognition.<sup>54</sup> The SSRIs and buspirone can improve anxiety.

*Motor dysfunction.* When significant parkinsonism is present in patients with DLB, the challenge for the clinician is to improve this feature without exacerbating psychotic symptoms, hypersomnolence, and orthostatism. Experience has shown that many of the parkinsonian signs and symptoms of DLB can respond to carbidopa/levodopa and the dopamine agonists, but they must be used cautiously. In an open label study, levodopa was generally well-tolerated but only a third experienced significant improvement in motor functioning.<sup>55</sup>

Levodopa therapy has not been shown to worsen daytime sleepiness.<sup>56</sup> In those with refractory depression warranting ECT, parkinsonism can improve through unknown mechanisms.

*Sleep disorders.* RBD is manifested as violent dreams/nightmares and potentially injurious dream enactment behavior, and the diagnosis is usually not difficult.<sup>29, 30, 34, 57, 58</sup> Yet patients with moderate to severe obstructive sleep apnea (OSA) can have features identical to RBD, the nightmares and behaviors are typically eliminated with nasal continuous positive airway pressure (CPAP).<sup>59</sup> Hence, patients should be considered for polysomnography (PSG) +/- nasal CPAP trial if there is a history suggesting RBD and/or OSA.

The goals of therapy for RBD are to minimize the nightmares and abnormal behavior, and since injuries to patients and their bedpartners can occur, treatment should be commenced in those with the potential for injury.<sup>29, 58, 60</sup> Simple measures to minimize the potential for injury involve counseling patients and their bedpartners move lamps and furniture away from the bed, and placing a mattress or cushion on the floor beside the bed. Clonazepam—the drug of choice for most RBD patients without dementia—is usually effective at 0.25-0.5 mg/night, although doses above 1 mg are sometimes necessary.<sup>29, 60-62</sup> Clonazepam is not an ideal agent in patients with dementia, but experience has shown that most patients tolerate the drug well at low doses.<sup>29, 60</sup> Melatonin can be effective at 3-12 mg/night either as monotherapy or in conjunction with clonazepam.<sup>63</sup> Since melatonin has a better tolerability profile than clonazepam in those with dementia, most clinicians use melatonin as first-line therapy for RBD in DLB or PDD.

Excessive daytime somnolence (EDS) can be caused by primary sleep disorders, depression, and medications as noted above, which may require PSG +/- multiple sleep latency tests (MSLT) to adequately evaluate.<sup>64</sup> Interestingly, there is evidence that some patients with Parkinson's disease and psychosis have narcoleptic-like features,<sup>65</sup> and the same may be true of DLB patients.<sup>29, 34</sup> Although one would hypothesize that psychostimulants would exacerbate hallucinations and delusions in patients with DLB, experience has shown that EDS as well as hallucinations and delusions can be well-managed with agents such as modafinil, armodafinil and methylphenidate.<sup>29, 64</sup> This is a controversial topic in the management of DLB, and clearly controlled trials will be necessary to justify use of psychostimulants in this population.

*Autonomic dysfunction.* Orthostatic hypotension (OH) can occur in DLB, which is likely due to degenerative changes in the intermediolateral cell column of the spinal cord and peripheral autonomic system.<sup>66, 67</sup> Liberalizing salt in the diet, salt tablets, thigh-high compression stockings, fludrocortisone, and midodrine are additional considerations. Although certainly not a first-line agent for management of OH, the cholinesterase inhibitors have recently been shown to improve OH.<sup>68</sup>

## **Parkinson Disease with Dementia**

### *Clinical features*

The diagnostic criteria for Parkinson disease with dementia (PDD) are shown in **Tables 2** and **3**. Most clinicians also follow the “one year rule” – if a patient develops parkinsonism, and at least one year later, the onset of dementia occurs, such patients are labeled as PDD. If dementia evolves within one year from the onset of parkinsonism, or if dementia precedes the onset of parkinsonism, then the label DLB is appropriate.<sup>3-5</sup>

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**Table 2. Features of dementia associated with Parkinson's disease**

### **I. Core features**

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
  - Impairment in more than one cognitive domain
  - Representing a decline from premorbid level
  - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

### **II. Associated clinical features**

#### 1. Cognitive features:

- Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
- Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)

- Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
- Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
- Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

2. Behavioral features:

- Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
- Changes in personality and mood including depressive features and anxiety
- Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
- Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
- Excessive daytime sleepiness

**III. Features which do not exclude PD-D, but make the diagnosis uncertain**

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

**IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D**

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
  - Acute confusion due to
    - Systemic diseases or abnormalities
    - Drug intoxication
  - Major Depression according to DSM IV
- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN

From reference<sup>69</sup>

**Table 3. Clinical criteria for diagnosis of probable and possible Parkinson's disease with dementia**

**Probable PDD**

A. Core features: Both must be present

B. Associated clinical features:

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

**Possible PDD**

A. Core features: Both must be present

B. Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
- Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. One of the group IV features present

From reference<sup>69</sup>

Many of the neuropsychological, neuroimaging, and neuropathologic features, as well as the management strategies, are very similar between DLB and PDD, and hence readers are encouraged to review the DLB section above for specifics. Since pimavanserin has recently been shown to be effective for hallucinations and delusions associated with Parkinson's disease psychosis<sup>53</sup>, this agent is increasingly being used in PDD with psychosis, but the expense of this drug must be considered.

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