WHITE PAPER

SYNUCLEINOPATHIES: DEMENTIA WITH LEWY BODIES

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Dementia with Lewy bodies (DLB) is one of the most common causes of dementia after Alzheimer's disease (AD) and vascular dementia. DLB can be difficult to diagnose, particularly in the early stages of the disease when there is a great deal of clinical heterogeneity. During this time, signs and symptoms can overlap with other causes of dementia.

At present, the only way to be certain about the diagnosis is to visualize the Lewy body pathology with immunohistochemistry in the neocortical structures of the brain at autopsy.

We would like to review current diagnostic criteria for DLB and then highlight the advances in being able to visualize supportive diagnostic pathology through a simple punch biopsy of the skin.

Cognitive dysfunction is often the presenting symptom in DLB. Unlike AD, which typically presents with memory loss as its first and most prominent cognitive deficit, DLB is characterized by early impairments in attention and executive and visuospatial function, with memory affected later in the course of the disease.[1,2] Early symptoms include difficulty driving a vehicle (e.g., getting lost, misjudging distances, or failing to see stop signs or other cars) and impaired job performance.

CORE CLINICAL FEATURES –

In addition to dementia, a patient with probable DLB must have at least two "core clinical features" of DLB: cognitive fluctuations, visual hallucinations, rapid eye movement (REM) sleep behavior disorder (RBD), and parkinsonism. These typically appear early and may persist throughout the disease course.[3]

1. **COGNITIVE FLUCTUATIONS** — Fluctuations in cognition and levels of alertness may occur early in the course of DLB and are estimated to be a feature in 60% to 80% of cases.[4] These episodes can be subtle, as in a brief decline in ability to perform an activity of daily living, or they may be dramatic enough to raise the question of a stroke or seizure. Caregivers often describe episodes in which patients appear to "blank out" or lose consciousness, become confused or behave in a bizarre manner, have speech or motor arrest, or become excessively somnolent.

2. **VISUAL HALLUCINATIONS** — Visual hallucinations occur in approximately two-thirds of patients with DLB, but are relatively rare in AD.[5] They are also an early sign in DLB and may precede parkinsonism. In one study with neuropathologic confirmation, visual hallucinations at presentation was the most useful clinical feature to distinguish DLB from AD, with 83% positive predictive value.[6]

3. **REM SLEEP BEHAVIOR DISORDER** — Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream enactment behavior that emerges after a loss of REM sleep atonia. Individuals have recurrent sleep-related vocalization and/or complex motor behaviors during REM sleep, correlating with dream mentation. The movements of RBD are short in duration (less than 60 seconds) and appear purposeful, such as throwing a ball or flailing to protect oneself. Sleep-related injuries can arise from jumping out of bed or striking a bed partner. RBD is commonly associated with DLB, occurring in 85% of individuals, often early in the course of the disease.[7] It can precede the clinical diagnosis of DLB by up to 20 years.

4. **PARKINSONISM** — Parkinsonian symptoms, such as bradykinesia, limb rigidity, and/or gait disorder, are seen in approximately 70% to 90% of patients with DLB.[8] However, parkinsonian features are usually more bilaterally symmetric and milder than in PD. Tremor may also occur, but it is much less common and less severe than in PD.

THERE ARE ALSO SUPPORTIVE FEATURES OF DLB.

1. **ANTIPSYCHOTIC SENSITIVITY** — Approximately 30% to 50% of individuals with DLB have severe sensitivity to antipsychotic drugs.9 Acute reactions include severe, sometimes irreversible parkinsonism and impaired consciousness, sometimes with other features suggestive of neuroleptic malignant syndrome. Adverse reactions are more common with first-generation antipsychotics but reactions to second-generation antipsychotics have also been described [35.[10]

2. **REPEATED FALLS** — Recurrent falls occur in up to a third of patients with DLB and may be among the earliest symptoms. Falls may seem to occur with or without provocation and may be related to parkinsonism, cognitive fluctuations, or orthostatic hypotension.

3. **SYNCOPE OR TRANSIENT LOSS OF CONSCIOUSNESS** — Episodes of altered or loss of consciousness are commonly described. Patients may transiently lose consciousness, or they may be awake but mute and staring blankly. Episodes may even resemble cataplexy, in which patients develop sudden atonia and fall to the floor.

4. **AUTONOMIC DYSFUNCTION** — Patients with DLB can exhibit autonomic dysfunction through urinary incontinence or retention, constipation and other gastrointestinal symptoms, and impotence.[11,12] Autonomic symptoms are more prevalent and severe than in PD, but less than in multiple system atrophy (MSA).

5. **HYPERSOMNIA** — Hypersomnia, also referred to as excessive daytime sleepiness, is common in patients with DLB and may be multifactorial. In addition to RBD, other sleep disorders that may be seen with DLB include insomnia, sleep apnea (obstructive or central), periodic limb movements of sleep, and restless legs syndrome.

6. **HYPOSMIA** — Decreased olfactory function is common in patients with DLB and other neurodegenerative dementias, including AD and Parkinson's disease.[13]

7. **HALLUCINATIONS IN OTHER MODALITIES** — Patients with DLB may also experience auditory hallucinations, which can be vague or well formed. Olfactory hallucinations can be pleasant (e.g., flowers or food) or unpleasant (e.g., burning rubber). Patients have described tactile hallucinations such as the feeling of insects on their skin or a cat brushing against their leg.

8. **SYSTEMATIZED DELUSIONS** — Delusions (false, fixed beliefs) occur commonly in DLB (in as many as 75% of cases) and may be elaborate, specific, and systematic.[14] They are often rooted in hallucinations or visual misperceptions that the patient has experienced. Common themes include: the spouse or caregiver is an impostor, the house is not their home, or people in the television or mirror are speaking to them or following them.

9. **APATHY, ANXIETY, AND DEPRESSION** — Most patients with DLB experience depressive symptoms at some point during their illness, and up to 40% have a major depressive episode. This is similar to the rate in PD,[15] but higher in one study than the rate seen in AD. Depression is less likely than other features of DLB to persist over time.

There are several indirect measures of Lewy body pathology that are indicative or supportive of the diagnosis in the proper clinical context. These include MRI scans that can display generalized atrophy with less hippocampal atrophy than AD.[16] SPECT and PET studies have been reported to show generalized decreased perfusion and metabolism, particularly in the occipital lobe areas.[17] DAT scans can demonstrate low dopaminergic activity in the striatum in DLB, but this can also be seen in MSA or progressive supranuclear palsy (PSP).[18] 123-I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy demonstrates low uptake in DLB, representing reduced postganglionic sympathetic cardiac innervation.[19] Similar abnormalities are also seen in PD, but not in MSA, PSP, or corticobasal degeneration.

Using these clinical features, a consensus criterion for the clinical diagnosis of DLB, developed by the Consortium on Dementia with Lewy Bodies, have been successively revised to improve sensitivity and specificity.[3]

CORE CLINICAL FEATURES FOR THE DIAGNOSIS OF DLB:

1) Fluctuating cognition with pronounced variations in attention and alertness

2) Recurrent visual hallucinations that are typically formed and detailed

3) REM sleep behavior disorder, which may precede cognitive decline

4) One or more cardinal features of parkinsonism (bradykinesia, rest tremor, rigidity)

SUPPORTIVE CLINICAL FEATURES:

1) Severe sensitivity to antipsychotic medications

2) Postural instability

3) Repeated falls

4) Syncope or other transient episodes of unresponsiveness

5) Severe autonomic dysfunction

6) Hypersomnia

7) Hyposmia

8) Hallucinations in other modalities

9) Systematized delusions

10) Apathy, anxiety, depression

INDICATIVE BIOMARKERS:

1) Reduced dopamine transporter uptake in basal ganglia by SPECT or PET

2) Abnormal 123Iodine MIBG myocardial scintigraphy

3) Polysomnographic confirmation of REM sleep without atonia

SUPPORTIVE BIOMARKERS:

1) Relative preservation of mesial temporal structures on MRI or CT

2) Generalized low uptake on SPECT/PET perfusion metabolism scan with reduced occipital activity

3) Prominent posterior slow wave activity on EEG with periodic fluctuations in the pre alpha/theta range

Using these criteria, patients can be placed into one of two categories:

PROBABLE DLB, DEFINED AS:

1) Two or more of the core clinical features of DLB are present, with or without active biomarkers.

2) One core clinical feature is present with one or more indicative biomarkers.

POSSIBLE DLB, DEFINED AS:

1) One core clinical feature of DLB is present with no indicative biomarker.

2) One or more biomarker is present, but no core clinical features.

CONCLUSIONS

What this complicated set of clinical and radiographic criteria highlight is that we do not yet have a single reliable diagnostic biomarker for DLB. At CND Life Sciences, we believe that the single best way to identify a patient with a synucleinopathy such as DLB is to visualize the abnormally folded synuclein. Using our proprietary methods and a decade of research, we can now confidently identify the abnormally folded synuclein within the dermal nerves from a simple punch biopsy of the skin. This test has high specificity and sensitivity in DLB. In a study of 30 patients, abnormally folded synuclein was present in all patients with DLB and in none of the disease or normal controls.[20]

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