

Lewy body Dementia: What are the challenges of early and accurate diagnosis?

A review of the neuroscience literature to inform clinical practice

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Abstract

Collectively, Lewy Body Dementia (LBD) including Parkinson's Disease Dementia (PDD) and dementia with Lewy Bodies (DLB) account for the second leading type of dementia following Alzheimer's disease (AD) (Lee et al., 2019). Despite revised consensus criteria, detection rates in routine clinical practice remain poor (Vann Jones & O'Brien, 2013) with cases commonly misdiagnosed as AD (McKeith et al., 2017).

Diagnosis can be challenging due to the presentation of an extensive range of autonomic, motor, sleep, cognitive and neuropsychiatric symptoms which can vary within a person and between individuals (Taylor et al., 2020). Given the disparity in management and prognosis of LBD compared to other dementias (Fujishiro et al., 2013), the timing and accuracy of diagnosis is of great consequence.

Key Words

Lewy Body Dementia – early diagnosis, neuropathology, neuroinflammation

Synthesis

CLINICAL CHARACTERISTICS

Core features for the clinical diagnosis of Dementia with Lewy bodies (DLB) include: fluctuations, hallucinations, parkinsonism and REM sleep behaviour disorder (Mc Keith et al., 2017). Fluctuations involve changes in attention, arousal and cognition including periods of inconsistent behaviour, unclear speech, variable attention, or altered consciousness (McKeith et al., 2017, p. 89). Visual hallucinations are a frequent "signpost" to

diagnosis occurring in 80% of patients with DLB (McKeith et al., 2017, p. 89). Hallucinations tend to be well formed, featuring animals, people, children and occasionally accompanied by sense of presence and sense of passage (McKeith et al., 2017). REM sleep behavior disorder (RBD) is exhibited by frequent acting out of dreams and movements

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resembling dream content and relates to an absence of REM sleep atonia (McKeith et al., 2017). Cardinal features of Parkinsonism include: resting tremor, rigidity and bradykinesia (slowness of movement) (Mc Keith et al, 2017)

Supportive clinical features include: postural instability, severe autonomic dysfunction, severe antipsychotic sensitivity, hyposmia (reduced sense of smell) delusions, anxiety, depression and apathy (McKeith et al., 2017). Additionally, transient episodes of unresponsiveness may serve as an intense form of cognitive fluctuation (McKeith et al., 2017). Autonomic dysfunction including: constipation, orthostatic hypotension and urinary frequency are thought to be more severe in DLB than AD (Bencze et al, 2020; Yamada et al, 2020). High-risk of neuroleptic sensitivity in this patient population limits the use of medications for the treatment of neuropsychiatric symptoms (Lee et al, 2019).

The “one-year rule” is used between the onset of dementia and parkinsonism for distinction between DLB and Parkinson’s Disease Dementia (PDD) (McKeith et al., 2017). Dementia that occurs concurrently or before parkinsonism should be diagnosed as DLB. Dementia that occurs in the background of well-recognised Parkinson’s disease (PD) should be termed PDD (McKeith et al., 2017).

This rule is recommended in research studies where distinction between DLB and PDD need to be made however, in the practice setting the generic term Lewy Body Dementia (LBD) can be more helpful since they are clinically similar diseases on a continuum (Mc Keith et al., 2017; Jellinger & Korczyn, 2018).

DIAGNOSTIC CHALLENGES

Diagnosis of LBD is largely based on the presence of characteristic symptoms however, many people with LBD do not present with all of these symptoms, especially at early stage and it can be difficult to distinguish from other forms of dementia, particularly Alzheimer’s disease (AD) (Mc Cleery et al., 2015; Chin et al., 2019).

Diagnosis of LBD using only clinical symptoms in some research has proven to be insensitive, relying on knowledge and skilled assessment from clinicians to make a formal diagnosis (Zweig and Galvin, 2014; Mc Cleery et al., 2015). The long-term nature and variance of prodromal states of LBD likely make it difficult to define the initial symptoms (Fujishiro et al., 2013). Additionally, atypical presentations are common, neuropsychological evaluation can be insufficient and available biomarkers are underused (Chin et al., 2019). Diagnostic accuracy and

specificity of diagnostic criteria in the clinical setting need further investigation (Yousaf et al., 2018).

Early and differential diagnosis of LBD from AD is critical for avoiding potentially harmful treatments, benefiting from cholinesterase inhibitors in early disease as well as accurately recruiting into clinical trials for potentially neuro-protective or disease modifying treatments (Fujishiro et al., 2013; Yousaf et al., 2018).

NEUROPATHOLOGY OF LBD

The main pathological hallmark of Lewy body dementias are Lewy bodies (LBs) (atypical aggregates of misfolded neurotoxic α -synuclein) that accumulate in the brain neurons (Walker et al., 2015; Lee et al., 2019; Londos et al., 2019). The mechanisms of LB genesis are not fully known but numerous hypotheses have been proposed including the Aggresome hypothesis (LB formation as a neuroprotective process for the removal of damaging proteins) and Autophagy Dysfunction causing neuronal loss and Increased Unfolded Protein Response (UPR) Activation (Olanow et al., 2004; Cuervo et al., 2004).

Severity of dementia in DLB is associated with the progression of LBs to neocortical and limbic structures and is an index for neuropathological diagnosis of LBD (McKeith et

al., 2017). LBs are not however, specific to DLB and their presence in other neurological disorders such as PDD and PD complicates diagnosis (Walker et al., 2015).

In DLB, LBs and Lewy neurites are present in the substantia nigra, whereas in a number of people with PD and severe cognitive impairment, Lewy neurites are found in the hippocampus (Spillantini & Goedert, 2006). Disorders with Lewy neurites and LBs therefore present as both a clinical and “neuropathological spectrum” (Spillantini & Goedert, 2006, p. 18). PD with minor cortical pathology or cognitive impairment sits at one end of the spectrum, while severe dementia with or without pre-existing Parkinsonism, is at the other end of the spectrum (Spillantini & Goedert, 2006).

On macroscopic observation, neuromelanin pigment loss in the locus coeruleus and substantia nigra are noted as well as mild cortical atrophy (Bencze et al., 2020). Microscopically, LBs in LBD and other neurodegenerative disorders feature a “central eosinophilic core surrounded by a peripheral halo” situated in the cell, causing disorder of subcellular organs (Bencze et al., 2020, p. 2).

Evidence for an association between increased relative glucose metabolism and dopaminergic deficiency in the limbic system

and basal ganglia regardless of cognitive impairment or disease duration was provided by Huber et al. (2020). In their cross-sectional analysis of a large multi-centre DLB cohort, Huber et al. (2020) demonstrated a slight increase in metabolic connectivity in the limbic system and basal ganglia at an early stage of dopamine deficiency, but declines significantly with intermediate or advanced nigrostriatal degeneration. This could suggest a disinhibition or compensatory mechanism by which metabolism increases in the somewhat dopamine depleted striatum (Huber et al., 2020). Although selection bias was towards a more complex DLB patient cohort in comparison to the general population, this study showed a clear link between disordered brain metabolism and the degree of dopaminergic cell loss in DLB (Huber et al., 2020). Identification of metabolic network changes at early stages of dopaminergic loss, prior to onset of motor symptoms, may prove useful as a supporting biomarker for the detection of DLB (Huber et al., 2020).

Aside from the dopaminergic system, cholinergic transmission also has a crucial role to play in the patho-mechanism of LBD, for example in the alteration of attention, arousal and memory (Bencze et al., 2020). Cholinergic deficits have been linked to delusions, hallucinations and cognitive impairment

(Klein et al., 2010; Creese et al., 2014). Since acetylcholine promotes wakefulness and alertness, the monoaminergic-cholinergic imbalance which reduces acetylcholine levels in LBD is thought to explain the extreme sleep patterns including; RBD, symptomatic narcolepsy and excessive daytime sleepiness (Perry et al 1990 as cited in Londos et al., 2019, p1.). Norepinephrine may also be implicated which explains interest in the cell loss of the locus coeruleus (Londos et al., 2019).

Lewy pathology in the peripheral nervous system could be an early phenomenon in LBD (Kon et al., 2020). Lewy pathology has been found in structures including; skin, retina, submandibular and adrenal glands, sympathetic and pelvic ganglia, cardiac sympathetic nerves and the enteric nervous system (Coon et al., 2018; Wakabayashi et al., 2010). This dissemination is thought to explain the clinical manifestations of thermoregulatory dysfunction, orthostatic hypotension, urogenital dysfunction and gastrointestinal dysmotility in LBD (Coon et al., 2018).

In 50% of autopsy-confirmed DLB cases, concomitant cerebrovascular pathology is frequently observed (Dugger et al., 2014). A larger number of microbleeds are reported in DLB than in AD however, the influence of vascular pathology to the clinical features of

LBD and its rate of progression requires further evaluation (Fukui et al., 2013).

NEUROINFLAMMATION IN LBD

Synucleinopathies are complicated disorders that advance through several stages with harmful α -synuclein aggregates spreading from cell to cell with prion-like behaviour (Valera & Masliah, 2015). The interaction between α -synuclein and microglia appears to be crucial in LBD with microglial activation suggesting a chronic inflammatory process (Surendranathan et al., 2015). Pathological studies confirm a role for inflammation with microglia demonstrating reactive states in the substantia nigra of PDD and PD cases together with LBs in conjunction with a minimization in dopaminergic cells (Surendranathan et al., 2015). Reducing inflammation and restoring neurotransmitter signalling (acetylcholine and dopamine) may prevent neuronal loss and alleviate symptoms however, this would ideally be more effective at the pre-symptomatic stage (Valera & Masliah, 2015) which would be a case for refining early detection and diagnosis. Through longitudinal studies of those at risk with established disease, studies could try to link the extent and nature of microglial activation with critical indexes of disease severity such as protein deposition, structural brain changes and the onset and advancement of core symptoms of

LBD (Surendranathan et al., 2015).

BIOMARKERS

The most decidedly refined ancillary test for DLB is "Dopamine Transporter (DAT) imaging using single-photon emission tomography (SPECT)", now considered a suggestive feature in the consensus diagnostic criteria (McCleery et al., 2015, p. 1). In a study of 22 participants in secondary care, DAT imaging accurately classified 100% of the subjects with DLB and 92% of the subjects who did not have DLB at post-mortem (Cromarty et al., 2016). The study sample was small though, DAT imaging remains costly and exposes patients to radioactivity (Cromarty et al., 2016). Additionally, this method provides little information regarding prognosis or disease progression (Cromarty et al., 2016).

Meta-iodobenzylguanidine (MIBG) Scintigraphy assesses cardiac postganglionic sympathetic degeneration, a prevalent feature in neurodegenerative diseases involving Lewy body pathology (Yousaf et al., 2018). Reduced uptake in iodine-123 MIBG scintigraphy is considered an indicative biomarker however, diabetes mellitus and autonomic neuropathy as well as congestive cardiac failure and ischemic heart disease need to be ruled out (Donaghy & McKeith, 2014).

On CT/MRI scans relative conservation of the

medial temporal lobe (MTL) structures is a supportive biomarker of DLB (McKeith et al., 2017). A more rapid clinical course may be predicted by considerable additional AD neuropathology change and MTL atrophy in DLB (Nedelska et al., 2015).

Resting state functional MRI (rsfMRI) investigates changes in functional brain connectivity in LBD showing greater activity during rest and diminished activity during cognitive tasks (Matar et al., 2019). The relatively small grey matter (GM) alterations shown in investigations of cortical thickness changes in DLB verify the concept that DLB results from dysfunction of neuronal synapses rather than neuronal loss (Yousaf et al., 2018).

Evidence is mounting to support quantitative EEG as an LBD biomarker and a potential neurophysiological marker for effectiveness of therapies to improve cognition (McKeith et al., 2017; van Dellen et al., 2015). In DLB, functional networks are characterised by loss of “network efficiency hubs” and diminished connectivity strength (van Dellen et al., 2015, p. 1). In a study of 66 probable DLB, and 66 probable AD patients and 66 controls it was found that the network in DLB becomes less well organised due to hub nodes losing their primary role in the network (van Dellen et al., 2015). Similarly, in a study of LBD and AD patients from old age psychiatry and neurolo-

gy services, alterations in dynamic properties in LBD indicated a brain state that is poorly responsive to environmental demands (Schumacher et al., 2019). This might explain the noticeable intermittent confusion and slowness in thinking that are typical in LBD (Shumacher et al., 2019). The higher temporal resolution provided by EEG compared to neuroimaging, may present improved etiological perspectives into the erratic perturbations in neurodegenerative disease brain networks (Cromarty et al., 2016).

Detection of lower levels of α -synuclein in the CSF of suspected DLB patients has proven potential benefit, particularly in discriminating from AD (Lim et al., 2013). Collection is invasive however, and it is not yet considered a reliable diagnostic tool with conflicting results due to blood contamination, and differences in CSF acquisition, analysis and processing (Mollenhauer & Schlossmacher, 2010). Similarly, detection of α -synuclein deposition in skin biopsies and blood need multi-centre studies and refined α -synuclein immunohistochemistry techniques (Yamada et al., 2020)

Confirmation of REM sleep without atonia via Polysomnography is an indicative biomarker of LBD due to high specificity for predicting Lewy-related pathology (Mc Keith et al., 2017).

Understanding of the core genes in LBD (ApoE4, GBA, SNCA, PARK2 and MAPT) remain limited with genetic studies being encouraged in research settings rather than in clinical settings where genetic testing for prediction of disease or confirmation of diagnosis would be premature (McKeith et al., 2017).

FUTURE DIRECTIONS

To assist in identification and diagnosis of LBD, two assessment toolkits were created as part of the DIAMOND Lewy Study (Thomas et al., 2018). The toolkits were piloted in Dementia and Parkinson's services within a single organisation to produce the final tools which proved to be acceptable to clinicians and patients (Thomas et al., 2016). Surendranathan et al. (2021) went on to introduce the final versions: "The Assessment Toolkit for Dementia with Lewy Bodies" (for Memory and Dementia clinicians) and "The Assessment Toolkit for Lewy Body Dementia" (for Movement disorders and Geriatric clinicians) (Thomas et al., 2018., p.1) into three movement disorder clinics and four Dementia clinics. This resulted in a compelling increase in the rate of diagnosis of DLB although this may have been due to the clinicians already being confident making the di-

agnosis (Surendranathan et al., 2021). Although further studies are needed in wider settings, the use of these instruments in routine clinical practice should enhance awareness of LBD symptoms and guide less experienced clinicians to identify key symptoms (Thomas et al., 2018).

To advance the 2017 "revised diagnostic criteria for DLB", future directions include 1) the development of criteria for prodromal and preclinical DLB to detect early disease, 2) evaluation of the specificity and sensitivity of the amended criteria through pathologically confirmed cases and 3) the institution of new biomarkers as well as additional classification of DLB-specific clinical features (Yamada et al., 2020, p.7). Longitudinal studies need to select at-risk groups (Donaghy & McKeith, 2014). Appraisal of clinical assessment tools and diagnostic thresholds for key features of LBD, will be crucial for determining quantitative clinical outcomes in future therapeutic and neuroprotective trials (Matar et al., 2019a).

Conclusion

The underlying neuropathology of LBD is not yet fully understood which makes accurate diagnosis and developing targeted treatments difficult (Lee et al., 2018). Literature shows that enhanced perception of cholin-

gic and dopamine deficiencies and brainstem and peripheral pathologies could help to establish the mechanisms of LBD as well as their diagnostic importance (Matar et al., 2018b). Advances in neuroimaging procedures can aid differential diagnosis (Yousaf et al., 2018). The detection of new biomarkers directly suggestive of Lewy-connected pathology can drive methods for possibly diagnosing LBD at the pre-clinical and prodromal stages which would have implications for optimising clinical care and management (Kane et al., 2018; Yamada et al., 2020). Since testing can be time consuming, invasive and expensive, further studies with larger multi-centre cohorts should be encouraged to substantiate the certainty of recent data and determine their feasibility and generalisability in clinical practice (Matar et al., 2019a).

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