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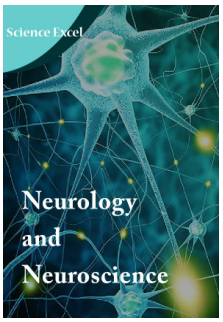
Review Article



The Essentials in Lewy Body Dementia

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dementia, Lewy bodies, neurodegeneration, diagnosis, treatment.

Abstract

Lewy body dementia (LBD) is an umbrella term describing two closely related conditions: Parkinson disease dementia (PDD) and dementia with Lewy bodies (DLB). LBD is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD), often underrecognized in clinical practice and accounting for approximately 4-7.5% of clinically diagnosed dementia cases but up to 20% of autopsy-confirmed dementia cases [1]. Neuropathologically, it is characterized by the accumulation of misfolded α-synuclein aggregates in neurons of the central and autonomic nervous systems and belongs to the group of synucleinopathies [2]. Core clinical features include progressive cognitive decline with marked fluctuations, recurrent visual hallucinations, REM sleep behavior disorder (RBD), and parkinsonism. Supportive features include severe neuroleptic sensitivity, autonomic dysfunction, postural instability, and recurrent falls [3]. The clinical presentation is heterogeneous and can overlap with AD and Parkinson's disease dementia (PDD), complicating differential diagnosis. In addition to Lewy bodies (LB), Alzheimer's disease co-pathology (beta-amyloid and tau deposits) is frequently present, contributing to diagnostic and clinical complexity [4]. The diagnosis of LBD is based on clinical criteria that include clinical manifestations and biomarkers, such as functional neuroimaging (PET or SPECT with dopamine transporter imaging), polysomnography (PSG), and ^{123}I-MIBG myocardial scintigraphy [5]. LBD exhibits genetic heterogeneity, with mutations in genes such as SNCA and GBA, and common risk factors such as APOE [6]. This condition typically manifests after age 60, although early-onset cases exist, posing a diagnostic challenge [7]. This review covers the key epidemiological, neuropathological, cognitive, behavioral, and biomarker characteristics of LBD and analyzes current treatment options.

Introduction

In autopsy studies, Okazaki et al. (1961) described the presence of Lewy bodies (LBs) in the cerebral cortex, brainstem, and spinal cord in two patients with dementia who died upon hospital admission. One of the patients had experienced progressive visual hallucinations during the year prior to admission. This finding marked the emergence of a new clinical entity and its distinctive anatomopathological correlate [8]. LBs are difficult to recognize in standard histological sections. In the 1980s, ubiquitin immunohistochemistry techniques led to greater understanding of the disorder. Polymeropoulos et al. (1997) demonstrated mutations in α-synuclein as a cause of autosomal dominant Parkinson's disease [9]. Spillantini et al. (1997) described the immunoreactivity of LBs for α-synuclein, improving their recognition and allowing a better understanding of the clinical features associated with LB pathology [10]. Lewy body dementia (LBD) encompasses two related clinical diagnoses: dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). Both share a common anatomopathological substrate: the aggregation of α-synuclein in the form of Lewy bodies (LBs) (Figs. 1 and 2) and Lewy neurites (LNs). No sign or symptom definitively distinguishes LBD from PDD. Current clinical criteria distinguish LBD from PDD solely by a one-year temporal requirement (the "1-year rule"). If dementia manifests more than 12 months after the onset of motor signs, it is classified as PDD. If dementia precedes or occurs concurrently with parkinsonism within one year of symptom onset, it is classified as LBD. The differentiation between LBD and PDD may be related to the sites of early α-synuclein aggregation and its subsequent propagation patterns.

Epidemiology

In autopsy series, DLB accounts for approximately 20% of dementia cases and has a prevalence similar to vascular dementia [12]. The population incidence of DLB in France was estimated at 1 per 1,000 persons per year [13]. Approximately 1.4 million Americans have DLB, 70% of them male, with a mean

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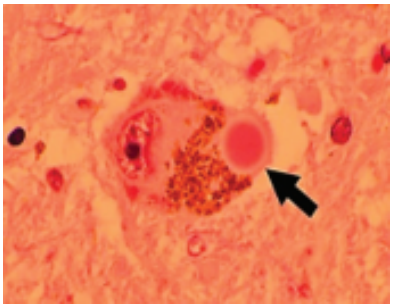

Fig. 1. Photomicrograph illustrating brainstem-type Lewy body in the substantia nigra (SN) (black arrow [11].

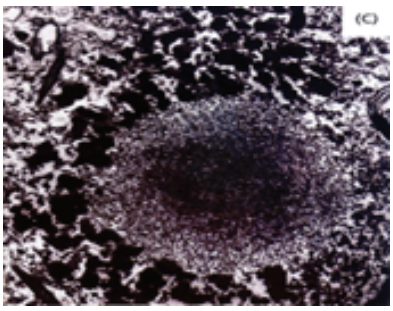

Fig. 2. Electron microscopy of the substantia nigra showing a Lewy body with an electron-dense filamentous central core and fibrillar rim [11].

age of symptom onset at 72 years. Compared to AD, patients with DLB more frequently report a history of depression and family history of Parkinson's disease (PD) [14]. The prognosis differs between DLB and AD. Survival of patients with DLB is shorter compared to patients with AD, and they are admitted to nursing homes 2 years earlier in the course of the disease [15].

Prodromal DLB

Prodromal DLB refers to a pre-dementia stage with signs or symptoms indicative of future DLB. Prior to cognitive decline, the patients often experience clinical symptoms common to synucleinopathies: 1-loss of smell (hyposmia), 2-autonomic dysfunction, 3-REM sleep behavior disorder (RBD), and 4-psychiatric disturbances. These prodromal features may present 15 years or more before the onset of dementia, making it difficult to distinguish early-stage DLB from other dementias, particularly AD. In a series of patients with RBD who subsequently developed DLB, the mean age of RBD onset was 61.5 years, while cognitive decline began at 68.1 years [16]. RBD may precede other symptoms of synucleinopathies or may manifest after cognitive decline has begun. Similarly, autonomic symptoms may precede DLB by many years [17]. Identification of prodromal DLB is essential, as it allows early detection and advance care planning, use of appropriate symptomatic medications, prevention of iatrogenic adverse events, and initiation of early intervention with emerging disease-modifying therapies before clinical symptoms cause disability. Research criteria for prodromal DLB have been applied to several subtypes, the most common being the mild cognitive impairment form. Less common presentations may include behavioral-onset, autonomic-onset, or psychiatric-onset (hallucinations /delusions) forms. Mild cognitive impairment due to DLB is characterized by a cognitive complaint that may be expressed by the patient, a family member, or the physician, with objective evidence of impairment in one or more cognitive domains and minimal impairment of activities of daily living. One or more of the core features of DLB are present, and some indicative biomarkers may also be positive at this stage [18].

Diagnostic Criteria

The diagnostic criteria are based on the Consortium for the Diagnosis of Dementia with Lewy Bodies Consensus, initially published in 2005 and most recently updated in 2017 (Table 1). The main change was relocating RBD to the core clinical criteria. These features may present in any order, but typically RBD precedes cognitive impairment, followed shortly by parkinsonism and hallucinations. Patients with DLB are also susceptible to delirium, frequently seen during hospitalization for acute intercurrent illness. DLB may present as rapidly progressive dementia [19]. An estimated 20% of DLB diagnoses are incorrect [20]. Distinguishing AD from DLB based solely on clinical findings is challenging, but the following features are significantly more common in DLB compared with AD: 1) cognitive fluctuations, 2) visual hallucinations (VH), 3) depression, 4) REM sleep behavior disorder, 5) agitation, 6) delusions, and 7) EEG abnormalities. Cognitive fluctuations, when associated with arousal disturbances and speech disorders, are highly characteristic of DLB as opposed to AD. VH constitute the strongest positive predictor for DLB diagnosis [21]. VH in DLB correlate with the presence of Lewy bodies in the temporal and occipital cortex. Another characteristic feature of DLB is the presence of REM sleep behavior disorder (RBD). In the context of dementia or parkinsonism, the presence of RBD often reflects an underlying synucleinopathy [22]. MRI studies have demonstrated greater cortical atrophy in patients with DLB compared to patients with PDD, suggesting that these two disorders represent distinct subtypes of LBD [23]. Medial temporal lobe (MTL) atrophy on MRI did not reliably differentiate between DLB and AD, although MTL atrophy is more severe in the latter [24].

Table 1. *Diagnostic Criteria for Dementia Syndrome Associated with Lewy Body Pathology (DLB) (McKeith IG, Boeve BF, Dickson DW) (2017) [25].*

Core Clinical Features
(The first three typically present early and may persist throughout the disease course).
1. Fluctuating cognition with pronounced variations in attention and alertness.
2. Recurrent complex visual hallucinations that are typically well-formed and detailed.
3. REM sleep behavior disorder, which may precede cognitive decline.
4. One or more spontaneous cardinal features of parkinsonism: bradykinesia (defined as slowness of movement), hypokinesia (decreased amplitude of movement), resting tremor, rigidity, and postural abnormalities (flexos hypertonus).
Supportive Clinical Features
Severe neuroleptic sensitivity to typical antipsychotics; postural instability; recurrent falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction (constipation, orthostatic hypotension, and/or urinary incontinence); hipersomnia; hyposmia; hallucinations in other sensory modalities (auditory, olfactory, gustatory, tactile); systematized delusions; apathy, anxiety, and depression.
Indicative Biomarkers
1. Reduced dopamine transporter uptake in the basal ganglia demonstrated by SPECT or PET imaging.
2. Abnormal (reduced uptake) 123-iodine-MIBG myocardial scintigraphy.
3. Polysomnography (PSG) confirmation of REM sleep without atonia.
Probable dementia with Lewy bodies can be diagnosed if:
1. Two or more core clinical features of dementia with Lewy bodies are present, with or without the presence of indicative biomarkers, or
2. Only one core clinical feature is present, but with one or more indicative biomarkers.
Probable dementia with Lewy bodies should not be diagnosed based solely on biomarkers.

MIBG: meta-iodobenzylguanidine; PET: positron emission tomography; REM: rapid eye movements; SPECT: single-photon emission computed tomography; PSG: polysomnography.

DLB is characterized by early and prominent deficits in visuospatial, executive, and attentional domains, in contrast to the marked episodic memory impairment that characterizes AD or the language definicits seen in primary progressive aphasia. Other suggestive features of DLB include depression, anxiety, apathy, hallucinations in other sensory modalities (auditory, olfactory, gustatory, or tactile), frequent falls, syncope, unexplained loss of consciousness, hyposmia, hypersomnia, constipation, orthostatic hypotension, and sensitivity to typical neuroleptics. The signs and symptoms of DLB may resemble AD, particularly in the early stages, but with careful evaluation, DLB can be distinguished from AD through the DLB consensus criteria and indicative biomarkers.

Neurobiology and Neuropathology of DLB

DLB is characterized by the intracellular accumulation of α-synuclein aggregates in the form of abnormal inclusion known as Lewy bodies (LBs) (Figs 1 and 2) and within neuronal processes as Lewy neurites (LNs). This histopathologic pattern defines a spectrum of disorders that includes Parkinson disease (PD), Parkinson disease dementia (PDD), and dementia with Lewy bodies (DBL) proper, whose clinical manifestations depend largely on the anatomic location of these inclusion bodies [26]. α-Synuclein, encoded by the SNCA gene, is a presynaptic protein involved in neurotransmitter release, vesicular fusion, and dopamine transport (DA). From a macroscopic standpoint, the most characteristic finding is observed in the substantia nigra (SN) of the midbrain, where there is significant loss of pigmented neurons, particularly in the ventral and lateral regions of the nucleus, as well as in the dorsal motor nucleus of the vagus, locus coeruleus, pedunculopontine nuclei, nucleus basalis of Meynert, amygdala, and hypothalamus. This pattern suggests a spread of neurodegeneration from the brainstem to limbic and neocortical structures. In cases of advanced DBL, signs of cortical vacuolization and microvacuolization may be observed, with spongiform changes in cortical layers I, II, and III, which in some cases progress to spongiform encephalopathy. Neuronal loss may reach up to 70% of pyramidal cells and is typically accompanied by gliosis and extracellular neuromelanin, indirect histological markers of neurodegeneration. At the microscopic level, the key finding is the presence of LBs, which appear as eosinophilic intracytoplasmic neuronal inclusions. Brainstem LBs are spherical and well-demarcated, with a dense eosinophilic core surrounded by concentric lamellar bands and a pale halo. They are readily visualized using hematoxylin and eosin staining. Cortical LBs, located in limbic and neocortical regions, are difficult to identify by routine staining and require specific immunohistochemical techniques to visualize α-synuclein. They are found in non-pyramidal neurons of the deep cortical layers, with a predilection for the insular cortex, amygdala, parahippocampal gyrus, and cingulate gyrus. From a structural standpoint, classic LBs show intermediate filaments arranged radially, associated with granular material and electron-dense vesicles, whereas cortical LBs exhibit

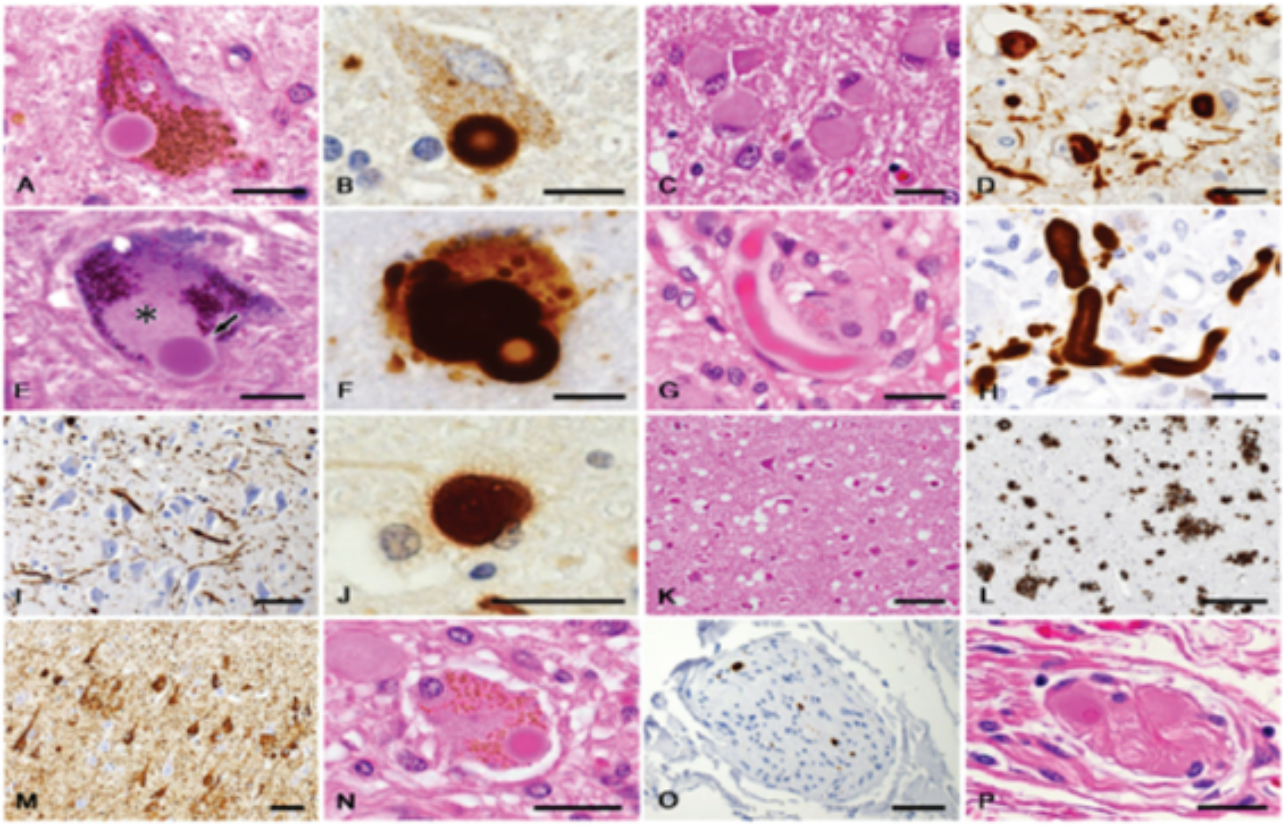

Figure 3. *Histopathology of dementia with Lewy bodies. A and B: Lewy bodies in dopaminergic neurons of the SN. C and D: Cortical-type Lewy bodies in the amygdala in dementia with Lewy bodies (DLB). E and F: Lewy bodies in the nervous system in Parkinson's disease (PD). G and H: Neurofibrillary tangles in sympathetic ganglia in PD. I: Neurofibrillary tangles in the hippocampal cortex in LBD. J: Glial inclusions in the nervous system in PD. K: Microvacuolation in the medial temporal cortex in DLB. L: Senile plaques in the hippocampal cortex in DLB. M: Neurofibrillary tangles in the hippocampus in DLB. N: Lewy bodies in a sympathetic ganglion in PD. O: Neurofibrillary tangles in cardiac sympathetic fibers in PD. P: Neurofibrillary tangles in the distal esophagus in PD. SN: sustantia nigra [83-84-85].*

wider, disorganized filaments with a felt-like appearance, lacking a central core. In the neuropil, thread-like structures (Lewy neurites), punctate structures (Lewy dots), or swollen axons (Lewy axons) may be found, collectively termed Lewy neurites (Fig.3). These abnormalities are observed not only in neurons but also in neuroglial cells (astrocytes and/ or oligodendrocytes) [27]. In addition to α-synuclein, LBs contain a wide variety of components, including: 1-stress response protein, 2-chaperones, 3-ubiquitin-proteasome system enzymes, 4-autophagy markers (such as p62), 5-lipids, 6-mitochrondrial fragments, 7-lysosomes, and 8-cytoskeletal components. Under pathological conditions, genetic, environmental, and aging-related factors promote destabilization, oligomerization, and assembly into insoluble filaments that presumably induce neurotoxicity. This heterogeneity in composition may explain the distinct staining patterns and morphological diversity: from classic eosinophilic bodies to pale bodies or even hematoxylin-eosin-negative bodies that are positive for other stains or lipophilic markers. The propagation of these inclusions follows an ascending pattern from the olfactory bulb and dorsal motor nucleus of the vagus toward pontine, mesencephalic, limbic, and cortical structures, in accordance with the stages proposed by Braak. This dissemination is considered dependent on synaptic connections and has been supported by findings in human neuronal transplants, where grafted neurons in patients with Parkinson disease developed LBs, suggesting a prion-like transmission mechanism [28]. In the preclinal phase, α-synuclein pathology is detected in the peripheral autonomic nervous system and adrenal medulla, although without clinical manifestations. In advanced stages, the pathology extends to the spinal cord, sympathetic ganglia, vagus nerve, gastrointestinal tract, and endocrine organs, with the highest density in the spinal cord and paravertebral sympathetic ganglia. At the genetic level, a close relationship has been identified between the number of copies of the SNCA gene and the clinical severity of the disease.

Mutations or duplications in this gene are associated with familial forms of DLB, whereas variants in genes such as GBA (related to lysosomal metabolism) and APOE ε4 increase the risk of developing the disease. Recently, other susceptibility loci have been proposed, such as BIN1 and TMEM175, shared in part with other dementias. The role of the immune system has been studied. Dysfunctional microglial activation has been reported, with increased expression of HLA-DR and CD68, not accompanied by cellular proliferation, suggesting an altered or senescent inflammatory response. The finding of dystrophic microglial processes and elevated levels of IL-6 in the hippocampus supports this hypothesis. DLB represents a complex neurodegenerative disorder in which mechanisms of protein misfolding and aggregation, disruption of cellular homeostasis, genetic susceptibility and dysregulated immune responses converge to drive disease pathogenesis [29].

Clinical Features of DLB

DLB is characterized by progressive cognitive decline, often indistinguishable from the cognitive disorder associated with PD, with a combination of cognitive, neuropsychiatric, motor, and autonomic symptoms demonstrating notable heterogeneity in presentation and course. Current diagnostic criterio distinguish between “core” and “supportive” clinical features. The core clinical features include: 1- cognitive impairment associated with marked cognitive fluctuations, with notable variations in attention and alertness that may occur over minutes, hours, or days; 2- recurrent visual hallucinations, typically well-formed and detailed, which are highly suggestive of DLB and occur in a significant proportion of patients (approximately 70% in some series); 3- spontaneous parkinsonism, which may manifest as bilateral akinetic-rigid syndrome, mild tremor, and gait disturbances, although up to one-third of patients may not exhibit parkinsonism in early stages; and 4- REM sleep behavior disorder (RBD), which may precede cognitive and motor symptoms and is associated with complex movements and vocalizations during sleep [30]. Not all patients manifest all core clinical features, and some of these may be transient or inconsistent throughout the disease course. The supportive clinical features include hypersensitivity to typical neuroleptics, frequent falls from standing height, syncope, autonomic dysfunction (orthostatic hypotension and/or urinary incontinence), depression, apathy, and delusions. Depression and apathy are common and may precede or accompany cognitive symptoms. The inclusion of indicative biomarkers can improve diagnostic accuracy. The presence of dementia, combined with two core features or one core feature and one indicative biomarker, is sufficient for a diagnosis of probable DLB; one core feature or one or more supportive features suggest a diagnosis of possible DLB. The definitive diagnosis of DLB is based on brain autopsy studies. These criteria allow for a sensitivity of 83% and a specificity of 95% for the presence of neocortical LBs. However, they do not reliably differentiate between pure DLB (approximately 20% of cases) and the more common mixed forms of DLB and AD (approximately 80% of cases). The differential diagnosis with AD and other dementias is complex, especially in early-onset cases, where motor and neuropsychiatric symptoms may be more prominent [31]. In summary, DLB is characterised by the triad of cognitive impairment with fluctuations, visual hallucinations and parkinsonism, frequently accompanied by RBD, and neuropsychiatric and autonomic symptoms. Clinical presentation may vary according to age at onset and the coexistence of other neurodegenerative pathologies, particularly AD [32].

Cognitive impairment and cognitive fluctuations in DLB

Cognitive impairment and cognitive fluctuations in DLB are distinct clinical phenomena thar are differentiable in clinical practice. Cognitive impairment refers to an insidious and continuous compromise of cognitive functions, typically with initial involvement of attention, executive functions, and visuospatial abilities, and a slowly progressive course, in contrast to the early stages of AD, characterized by recent episodic amnesia [33]. This impairment is similar to that observed in other dementias, although with a neuropsychological profile characteristic of DLB. Patients demonstrate difficulties on tasks such as the Trail Making Test, semantic verbal fluency, and verbal learning tests, with these instruments being useful for early detection and monitoring of cognitive impairment [34]. DLB is characterized by a neuropsychological profile of cortical (visuospatial ability, memory, and language) and subcortical (learning, attention, visuoconstructive ability, and psychomotor speed impairment). The rate of cognitive decline in patients with DLB, AD, or vascular dementia is similar. Cognitive fluctuations constitute one of the core features of DLB and manifest as spontaneous and marked variations in the level of attention, alertness, and cognitive performance, which may develop over the course of hours, days, or even weeks and are not explained by any external factor. Clinically, these fluctuations are distinguished by episodes of daytime somnolence, periods of acute confusion, abrupt changes in the level of consciousness, and transitory alterations in speech and

functional capacity, such as "staring into space" or "producing disorganized speech" [35]. These manifestations are usually intermittent and of spontaneous onset and resolution, in contrast to gradual cognitive decline, which is persistent and progressive. Clinical differentiation is supported by direct observation, patient interview, and, fundamentally, caregiver report: caregivers can identify episodes of cognitive fluctuation that may not be detected during an initial consultation [36]. Instruments such as the Dementia Cognitive Fluctuation Scale and specific questionnaires allow these fluctuations to be objectified, evaluating items such as daytime somnolence, functional variability during the day, and alterations in the level of consciousness. Accurate identification of these fluctuations requires systematic clinical evolution, the use of specific scales, and integration of information provided by caregivers [37].

Neuropsychiatric Disorders

Patients may manifest: 1. Visual Hallucinations: Well-formed, recurrent, and complex, which may involve people, objects, or animals, in color or black and white, and are usually vivid, detailed, and persistent, producing fear in the patient, although the patient retains awareness of their lack of reality. Hallucinations in other sensory modalities (auditory, olfactory, gustatory, or tactile) may occur less frenquently. 2. Delusions: Patients may present with misidentification delusions (believing that a family member has been replaced by an impostor), paranoide delusions (persecution), and delusions related to the physical environment. The presence of multiple delusion subtypes is more frequent in DLB than in other dementias. 3. Cognitive fluctuations: Marked variations in attention and level of consciousness are observed, which may simulate an acute confusional state or delirium, without a clear precipitating cause. 4. Affective disorders: Depression, anxiety, and apathy are frequent and may present from the prodromal phase. Depression may be more prominent in early-onset dementia with Lewy bodies, and apathy is considered a supportive feature in the diagnostic criteria [38-39]. 5. Sensitivity to typical antipsychotics (postsynaptic D2 receptor blockers) are described, characterized by severe akinetic-rigid syndrome that can lead to prostration. 6. Agitation, irritability. Unlike AD, DLB presents with greater frequency and severity of visual hallucinations, complex delusions, cognitive fluctuations, and affective disorders, in addition to a cognitive profile with impairment of attention, executive functions, and visuospatial abilities. The coexistence of AD pathology may increase the burden of neuropsychiatric symptoms, especially hallucinations and agitation [40].

Sleep Disorders

Sleep disorders associated with DLB are frequent, complex, and precede the onset of cognitive symptoms. The most characteristic and relevant is RBD, which is considered a core clinical marker and pathognomonic feature of DBL. This disorder involves the loss of muscle atonia during REM sleep and leads patients to act out their dreams, often with abrupt movements and vocalizations, potentially injuring themselves or their bed partners [41]. RBD may precede the onset of dementia by years; its confirmation is made through nocturnal polysomnography and constitutes a diagnostic criterion for dementia with Lewy bodies. Other sleep alterations are observed: 1- Poor subjective sleep quality and nocturnal sleep fragmentation, with frequent awakenings and difficulty maintaining sleep, 2- Hypersomnia or excessive daytime sleepiness, more prominent in DLB than in other dementias, associated with the characteristic cognitive fluctuations of the disease, 3- Alterations in sleep architecture, such as the absence of sleep spindles and K-complexes, delta activity during REM sleep, and slowing of EEG activity in the occipital region during wakefulness, 4- Abnormal nocturnal behaviors related to other disorders such as obstructive sleep apnea or periodic limb movements (PLM). Compared with AD, sleep disorders in DLB are more frequent and severe, especially RBD and daytime sleepiness [42-43].

Motor involvement

Motor involvement in DLB, progresses throughout the disease course. In the prodromal and early phases, motor symptoms may be subtle and precede clinical diagnosis by several years. Bradykinesia and hypokinesia typically manifest, followed by rigidity and tremor, the latter generally being action tremors and less frequently resting tremors, with less asymmetry than in idiopathic PK. In this initial stage, gait disorders and postural instability are frequent, even exceeding those observed in PK and are associated with a greater risk of falls from standing height [44]. With the progression of DLB, motor involvement becomes more pronounced, with predominance of the akinetic-rigid subtype, and the patient manifests difficulty rising from a chair, hypomimia, bodily bradykinesia, and axial rigidity [45]. Postural instability and gait disorders become prominent, as do falls. Tremors are usually bilateral, mild, and symmetric. Motor progression in DLB is more rapid than in PK, especially in the domains of gait and limb bradykinesia. Regarding the neurophysiological correlate, both in the prodromal phase and in established dementia, dysfunction of GABAergic and glutamatergic circuits is observed in association with motor deficits, while cholinergic dysfunction correlates primarily with cognitive impairment [46]. The severity of motor symptoms in DLB does not necessarily correlate with age, disease duration, or degree of cognitive impairment, unlike what occurs in PK. Based on the foregoing, motor involvement in DLB Lewy bodies adopts an akinetic-rigid pattern with marked postural instability and gait disturbance in advanced stages, with more rapid progression than in other synucleinopathies and relatively less tremor and asymmetry [47].

Supportive clinical features

Hypersensitivity to typical antipsychotics manifests as a marked akinetic-rigid response associated with a confusional state following exposure to a typical neuroleptic drug with blocking effect on postsynaptic D2 receptors (D2R). If necessary, administration of atypical neuroleptics should be considered (quetiapine, clozapine, and/or pimavanserin). Severe autonomic dysfunction is observed, characterized by constipation, orthostatic hypotension, and/or urinary incontinence. Patients may present hallucinations involving other sensory modalities (auditory, olfactory, gustatory, or tactile). During the course of DLB, patients develop severe postural abnormalities and recurrent falls that must be differentiated from syncopal episodes. Hyposmia manifests in the early phase of DLB.

Biomarkers in DLB

The 2017 revision of the diagnostic criteria for dementia with Lewy bodies incorporates various biomarkers to increase diagnostic specificity, defined as indicative and supportive biomarkers. These biomarkers allow for the objective demonstration of the following findings: 1-reduced dopamine transporter uptake in the basal ganglia, demonstrated by SPECT or PET, 2-reduced cardiac uptake of metaiodobenzylguanidine ([123I] MIBG) on myocardial scintigraphy, 3-absence

of atonia during REM sleep, demonstrated by nocturnal polysomnography. These biomarkers are considered "indicative" and can support the diagnosis when only one core clinical feature is present, although they are not specific to dementia with Lewy bodies [48]. Current biomarkers in dementia with Lewy bodies include: 1-Dopaminergic SPECT/PET imaging, 2-Cardiac ^123I-MIBG scintigraphy, 3-Polysomnography (overnight PSG), 4-Cerebrospinal fluid (CSF) α-synuclein assays, 5-Plasma and CSF β-amyloid and phosphorylated tau (including p-tau217), 6-Plasma glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL), 7-FDG-PET metabolic patterns, 8-Detection of phosphorylated α-synuclein in skin biopsy and 9-Mitochondrial DNA methylation analysis in peripheral blood.Their combined use improves diagnostic accuracy and allows for patient stratification according to co-pathologies [49]. Detection of α-synuclein aggregates in CSF using seed amplification assays (SAA) has demonstrated high diagnostic value in DLB, even at prodromal stages [50]. This technique identifies pathological α-synuclein species with sensitivity and specificity exceeding 90%, differentiating DLB from non-synucleinopathic dementias. Furthermore, kinetic parameters derived from these assays may provide prognostic information regarding disease progression [51]. Measurement of β-amyloid and phosphorylated tau in plasma and CSF in DBL plays a fundamental role in identifying Alzheimer's disease co-pathology, refining stratifying prognosis, and guiding clinical management. The presence of β-amyloid is associated with greater cognitive decline, and the presence of tau with lower frequency of motor symptoms and REM sleep disorders [52]. Elevated plasma levels of glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) in DLB indicates astrocytic damage and activation (astrogliosis) and axonal degeneration respectively and reflects underlying pathological processes common in DLB and other neurodegenerative diseases, although not specific to DLB [53]. Regarding diagnostic imaging studies, the metabolic pattern in DLB, on PET allows differentiation of DLB from controls and from AD, even in prodromal stages, and correlates with clinical severity [54]. The current role of positron emission tomography (PET) imaging for alpha-synuclein detection in DLB is primarily experimental and is not available in clinical practice [55]. Blood mitochondrial DNA methylation, specifically in the D-loop region, should be considered a promising epigenetic biomarker for detecting cellular stress and energy dysfunction in patients with MCI, independent of amyloid burden [56]. D-loop methylation reflects alterations in mitochondrial homeostasis and oxidative stress, processes central to the pathophysiology of MCI and other neurodegenerative diseases [57]. In skin biopsy studies using Real-Time Quaking-Induced Conversion techniques, a minimally invasive technique (through a skin punch), skin nerves are analyzed, allowing for early and objective diagnosis (Fig. 4), which detects phosphorylated α-synuclein in dermal nerve fibers. This procedure achieves a sensitivity exceeding 93%, enabling diagnosis in prodromal stages [58-60].

Cardiac ^123I-MIBG abnormalities reflect reduced noradrenergic innervation of the myocardium in DLB. However, similar findings may be observed in other conditions affecting autonomic fibres, such as diabetes mellitus (Fig. 5) [61].

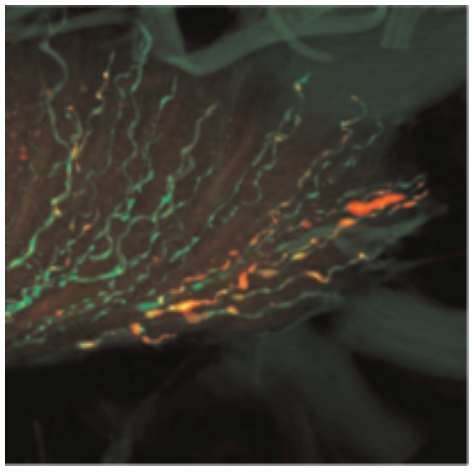

Figure 4. *Skin biopsy from a patient with DLB. The green fluorescent signals represent peripheral nerves. The red fluorescent signal represents positive staining for phosphorylated α-synuclein [68].*

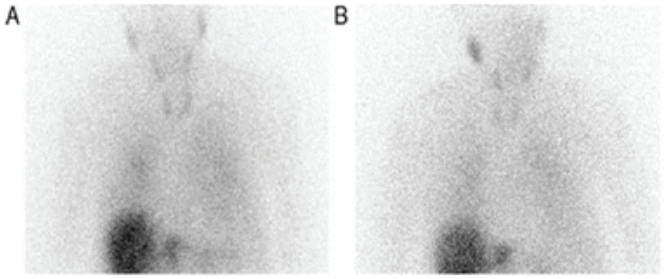

Figure 5. *Patient with DLB studied by myocardial scintigraphy. A marked decrease in myocardial uptake of metaiodobenzylguanidine ([123I] MIBG) is observed in the early phase [67].*

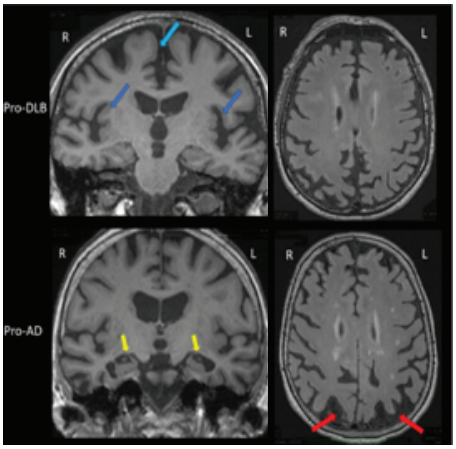

Figure 6. *MRI images in the coronal and axial planes in DLB and prodromal AD. Upper left image: T1 sequence, coronal. Blue arrows show bilateral insular atrophy and frontomesial atrophy (light blue arrow). Upper right image: FLAIR sequence, axial. No ischemic vascular lesion is present. Note the right parietal atrophy. Lower left image: T1 sequence, coronal. Yellow arrows show bilateral hippocampal atrophy, predominantly on the left. Lower right image: FLAIR sequence, axial. Red arrows show bilateral parietal atrophy. Greater hippocampal atrophy is observed in AD and greater insular and frontomesial atrophy in DLB [64].*

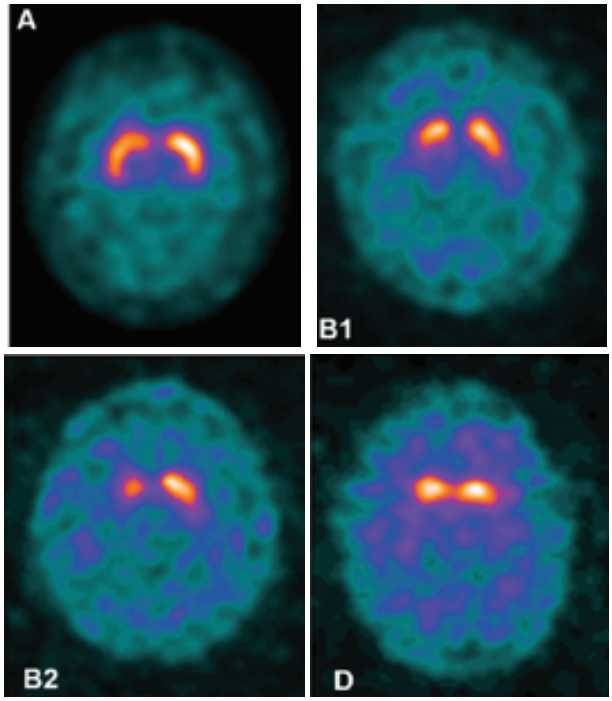

Figure 7. *DAT-SPECT (Single Photon Emission Computed Tomography of Dopamine Transporters). A: Normal finding with symmetric tracer uptake in the caudate nucleus and putamen, with "comma" morphology. B1: mild asymmetric putaminal reduction. B2: moderate asymmetric putaminal reduction, with marked loss of activity in the right putamen. D: bilateral loss of DAT signal in the putamen, with relative preservation of the caudate nucleus, generating a "dot" or "egg" morphology [66].*

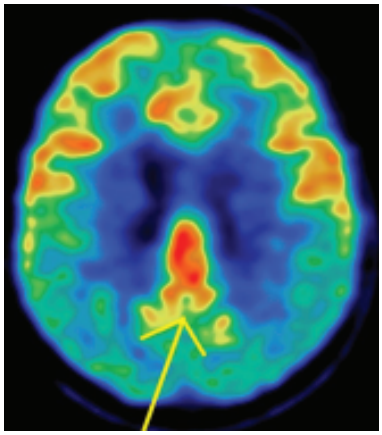

Figure 8. *PET-CT in a patient with DLB. Hypometabolism in the bilateral occipital lobes (orange arrows). Preservation of uptake in the posterior cingulate cortex: cingulate island sign (yellow arrow) [65].*

Magnetic resonance imaging (MRI) in patients with cognitive impairment typically demonstrates bilateral hippocampal atrophy in AD, whereas patients with DLB more often exhibit fronto-mesial cortical atrophy (manifested by widening of the anterior interhemispheric fissure) and bilateral insular cortical atrophy (Fig. 6). Dopamine transporter imaging with ^123I-ioflupane SPECT (DaTSCAN) assists in differentiating DLB from AD, particularly when clinical findings or PET results are inconclusive. In DLB, striatal hypouptake is observed and may be symmetrical, in contrast to Parkinson's disease dementia (PDD). Abnormal uptake typically begins in the posterior putamen and, with disease progression, extends to involve the entire striatum, including the caudate nucleus (Fig. 7) [62].

FDG-PET studies commonly demonstrate occipital hypometabolism, particularly in patients with visual hallucinations. This may be accompanied by relative preservation of posterior cingulate metabolism, producing the so-called cingulate island sign (Fig. 8). Occipital hypoperfusion and the cingulate island sign may help differentiate DLB from other types of dementia, especially AD. In the absence of occipital involvement, distinction between DLB and AD may be challenging [63]. Generalized slow-wave activity on EEG constitutes another supportive biomarker.

Proposed Diagnostic Approach

In patients with suspected DLB, a practical stepwise approach may include: 1-Blood testing for p-tau217 (to assess underlying AD pathology) and plasma NfL (to estimate neurodegenerative severity), 2-Skin biopsy for detection of phosphorylated α-synuclein to confirm Lewy body pathology, 3-CSFα-synuclein seed amplification assay (optional), particularly if skin biopsy findings are inconclusive.

Collectively, these biomarkers provide complementary information, enabling earlier and more accurate diagnosis, improved prognostic stratification and a more individualised therapeutic strategy.

Therapeutic considerations

Cognitive symptoms

Acetylcholinesterase inhibitors (AChELs) (donepezil, galantamine, and rivastigmine) are particularly useful in the treatment of DLB. They inhibit the degradation of acetylcholine in the synaptic cleft, thereby prolonging its effect on cholinergic receptors. They are usually well tolerated at standard doses and appear to be more effective in patients with DLB than in those with AD, due to the early and prominent cholinergic dysfunction of the central nervous system chracteristic of DLB. Several clinical trials and meta-analyses evaluating AChEIs suggest that these agents may improve cognitive domains without producing significant changes in motor symptoms. AChEIs are approved by the US Food and Drug Administration (FDA) for the treatment of Parkinson's disease dementia (PDD) and are frequently prescribed off-label for DLB.The most common adverse effects of AChEIs are gastrointestinal, including nausea, vomiting, diarrhea, anorexia and weight loss. Other reported side effects include insomnia, vivid dreams, leg cramps and urinary urgency. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved for the treatment of cognitive impairment in AD. However, it has not been evaluated in large-scale, randomised controlled trials in patients with PDD or DLB. Available evidence from case reports and small case series in PDD and DLB has yielded variable results [69].

Sleep disturbances

Persistent sleep disturbance constitutes a core feature of DLB. Melatonin represents the first-line treatment, with a dose ranging from 3 to 20 mg at bedtime [70]. Clonazepam, a long-acting benzodiazepine, constitutes a second-line therapy that is generally initiated at the lowest possible dose, due to its negative impact on falls, dizziness, somnolence, and confusion. It should be prescribed with caution in older adults with DLB [71]. Most of the evidence supporting the use of melatonin and

clonazepam derives from case series and observational studies rather than large placebo-controlled trials. Other sleep disorders include obstructive sleep apnea (which may be confused with REM sleep behavior disorder), restless legs syndrome, and periodic limb movements during sleep, which usually respond to dopamine agonists (pramipexole or ropinirole) [72].

Motor symptoms

There are no large randomised controlled trials specifically addressing the treatment of motor symptoms in patients with DLB, although case series suggest that low-dose levodopa (approximately 300 mg/day), administered in combination with carbidopa or benserazide, may provide modest improvement in parkinsonian features. Levodopa, as well as dopamine agonists, may precipitate or exacerbate psychosis. Nevertheless, levodopa should not be withheld solely on the basis of cognitive impairment. In DLB, the risk of psychotic symptoms is higher than in Parkinson's disease (PD), and because motor symptoms are often relatively mild, treatment of parkinsonism should generally be reserved for cases in which motor impairment significantly interferes with activities of daily living. Monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, dopamine agonists, anticholinergic agents and amantadine may worsen cognitive and behavioural symptoms and should therefore be avoided or used with extreme caution in patients with DLB [73].

Autonomic symptoms

Orthostatic hypotension occurs in approximately 45% of patients with DLB. Midodrine and fludrocortisone are the most commonly used medications. Midodrine is administered at doses of 5-10 mg three times daily, avoiding use near bedtime due to the risk of supine hypertension. Fludrocortisone is initiated at 0.1 mg/day, with a maximum of 0.2-0.3 mg/day, monitoring adverse effects such as edema, hypokalemia, and hypertension. For urinary symptoms, such as overactive bladder, β3 agonists, such as mirabegron, reduce symptoms with fewer cognitive adverse effects compared to antimuscarinic medications (oxybutynin), which should be avoided because they tend to exacerbate cognitive deficits [74].

Behavioral symptoms

Behavioral symptoms such as hallucinations, delusions, mood disorders (anxiety, depression, apathy), and agitation or aggression are frequently observed in DLB. Non-pharmacological strategies should be considered first-line and include careful evaluation for physical conditions that may precipitate behavioural disturbance, such as urinary retention, fecal impaction, pain or pressure ulcers. Potentially aggravating medications should be reviewed and reduced or discontinued where possible. When medication is required to mitigate behavioral symptoms, it should be prescribed at low doses for the shortest possible time, avoiding benzodiazepines (risk of sedation and paradoxical agitation) and tricyclic antidepressants (anticholinergic effects). In cases of non-distressing hallucinations that do not pose a risk to the patient, pharmacological intervention may not be necessary [75]. Typical antipsychotics should be avoided in DLB, as they may significantly worsen motor function and can precipitate severe neuroleptic sensitivity reactions. When antipsychotic treatment is unavoidable, atypical agents are preferred. Clozapine has long been employed in Parkinson's disease psychosis and may benefit patients with DLB; however, its use is limited by the need for hematological monitoring (risk of agranulocytosis), initially weekly and subsequently monthly, which complicates its use. Risperidone and olanzapine at low doses are usually well tolerated; however, motor complications (rigidity or bradykinesia) may be observed with high doses in the long term. Several case reports and case series suggest possible behavioral benefits of aripiprazole and brexipiprazole in DLB, however, their partial agonist effect on postsynaptic dopamine D2 receptors may induce motor complications [76]. Pimavanserin, a selective serotonin 5-HT2A and 5-HT2C receptor inverse agonist/antagonist, reduces delusions and hallucinations in PDD and has been approved by the US Food and Drug Administration (FDA) for the treatment of psychosis in PD [77]. It has no affinity for dopaminergic, adrenergic, histaminergic or muscarinic cholinergic receptors in the central nervous system. Consequently, it does not exacerbate motor symptoms, does not cause sedation, does not impair cognition and lacks many of the adverse effects associated with atypical antipsychotics. Although not yet supported by large randomised clinical trials in DLB, clinical experience suggests sustained efficacy in the treatment of neuropsychiatric symptoms. It is administered as a single 34 mg nocturnal dose and does not require titration [78]. When prescribing antipsychotics, clinicians should remain vigilant for adverse effects, including: 1-Excessive sedation, 2-Orthostatic hypotension, 3-Paradoxical behavioural worsening.

Discussion

A new classification and staging framework based on biological "anchors" has recently been developed for DLB. The proposed system called the Neuronal α-Synuclein Disease Integrated Staging System (NSD-ISS), is founded upon two biological anchors: (1) the in vivo detection of pathological α-synuclein (S anchor), defined by cerebrospinal fluid (CSF) seed amplification assays; and (2) neuronal dopaminergic dysfunction (D anchor), defined by abnormal dopamine transporter SPECT imaging. This framework redefines the disease from a biologically driven perspective, capitalising on advances in biomarker research and establishing stages that range from asymptomatic biomarker positivity to progressively increasing degrees of functional impairment [79-80]. The NSD-ISS includes various stages 0–1 (absence of clinical symptoms with biomarker positivity), stage 2 (subtle symptoms without functional impairment), and stages 2B–6 (clinical manifestations with progressive functional decline), integrating both clinical and biomarker data. At present, the NSD-ISS is not approved for routine clinical use and remains restricted to research settings, particularly in the design of clinical trials and patient selection. Classical neuropathological staging systems—such as Braak staging, the McKeith criteria, the Unified Staging System and the more recent Lewy pathology (LP) Consensus Criteria—continue to represent the reference standards for post-mortem evaluation and clinicopathological correlation. However, they do not incorporate the concept of biological "anchors" into routine clinical practice [81-82].

Conclusions

DLB constitutes the second leading cause of neurodegenerative dementia after AD, characterized by a distinctive clinical presentation of motor, cognitive, behavioral, affective, and autonomic symptoms. PDD and DLB share similar neuropsychological profiles that distinguish them better from AD than from each other. Both conditions share a common pathological substrate—namely, the accumulation of α-synuclein in the form of Lewy bodies (LBs) and Lewy neurites (LNs) within neocortical, limbic, subcortical and brainstem regionsaccounting, at least in part, for the core clinical

features of DLB. There remains ongoing debate as to whether PDD and DLB should be regarded as distinct clinical entities, with differences reflecting regional patterns of pathological involvement, or as part of a unified spectrum of α-synuclein aggregation disorders. The one-year rule continues to serve as a pragmatic and clinically useful distinction in both research and practice, although it may ultimately be superseded by a more objective staging system. The development of biologically informed staging frameworks, combined with deep phenotypic characterisation of prodromal stages (e.g. anosmia and REM sleep behaviour disorder), will enhance understanding of disease mechanisms and facilitate the development of novel therapeutic strategies. Indicative biomarkers are increasingly being refined to improve diagnostic accuracy in DLB. Each currently available biomarker provides an indirect measure of neuronal injury and neurodegeneration. Direct quantification of pathological α-synuclein in CSF, skin, plasma and, potentially, through molecular PET imaging may prove transformative. These advances, together with the implementation of standardised assessment tools, are likely to enhance diagnostic precision in clinical practice and contribute to the development, testing and validation of new disease-modifying therapies..

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