Dementia with Lewy bodies

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Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia in older people, accounting for 10% to 15% of all cases. It occupies part of a spectrum that includes Parkinson's disease and primary autonomic failure. All these diseases share a neuritic pathology based upon abnormal aggregation of the synaptic protein α-synuclein. It is important to identify DLB patients accurately because they have specific symptoms, impairments, and functional disabilities that differ from other common dementia syndromes such as Alzheimer's disease, vascular cognitive impairment, and frontotemporal dementia. Clinical diagnostic criteria for DLB have been validated against autopsy, but fail to detect a substantial minority of cases with atypical presentations that are often due to the presence of mixed pathology. DLB patients frequently have severe neuroleptic sensitivity reactions, which are associated with significantly increased morbidity and mortality. Cholinesterase inhibitor treatment is usually well tolerated and substantially improves cognitive and neuropsychiatric symptoms. Although virtually unrecognized 20 years ago, DLB could within this decade become one of the most treatable neurodegenerative disorders of late life.

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Dementia with Lewy bodies (DLB) is probably the second most prevalent cause of degenerative dementia in older people; only Alzheimer's disease (AD) is more common. For example, a recent community study of 85+ year olds found 5.0% to meet clinical diagnostic criteria for DLB, representing 22% of all demented cases.[1] Despite its high prevalence, DLB was only fully recognized about a decade ago, as a result of improved methods of neuropathological staining, which allowed the key lesions (Lewy bodies [LBs]) to be seen in autopsy brain tissue.[2] It is therefore a relative newcomer for many clinicians, for whom it poses significant difficulty in antemortem diagnosis. The importance of recognizing DLB relates particularly to its pharmacological management, with reports of good responsiveness to cholinesterase inhibitors,[3] but extreme sensitivity to the side effects of neuroleptics.[4,5] This article, which reviews current knowledge and opinion about DLB, is based upon the deliberations of two recent international consensus meetings.[6,7]

Diagnostic concepts

DLB has carried a variety of diagnostic labels during the last two decades, including diffuse Lewy body disease (DLBD),[8] Lewy body dementia (LBD),[9] the Lewy body variant of Alzheimer's disease (LBVAD),[10] senile dementia of Lewy body type (SDLT),[11] and dementia associated with cortical Lewy bodies (DCLB).[12] This multiplicity of terms reflects the coexistence in the brains of these cases of α-synuclein–positive LBs and Lewy neurites (LNs) and abundant Alzheimer-type pathology, predominantly in the form of amyloid plaques. Tau-positive inclusions and neocortical neurofibrillary tangles sufficient to meet Braak

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stages V or VI occur in only a minority of cases *(Figure 1)*. Alzheimer pathology is not a prerequisite for the existence of dementia however, since cases with "pure" LB disease may present clinically with cognitive impairment and other neuropsychiatric features. Nor is the number of cortical LBs robustly correlated with either the severity or the duration of dementia,[13,14] although associations have been reported with LB and plaque density in mid-frontal cortex.[15] LN and neurotransmitter deficits are suggested as more likely correlates of clinical symptoms.[14,16] α-Synuclein immunoreactive deposits with many of the characteristics of LBs have also been reported in a high proportion of AD cases, particularly in the amygdala.[17] In this context, they may represent an end-stage phenomenon, with secondary accumulation of aggregated synuclein in severely dysfunctional neurones that are already heavily burdened by plaque and tangle pathology.[18] Whatever the explanations are for this considerable overlap in pathological lesions in DLB and AD, it is clear that clinical separation of cases is going to be less than 100% precise. The presence of Alzheimer pathology in DLB appears to modify the typical clinical presentation making such cases harder to differentiate clinically,[19] with the core features (see below) being scant or absent and the clinical picture more closely resembling AD.

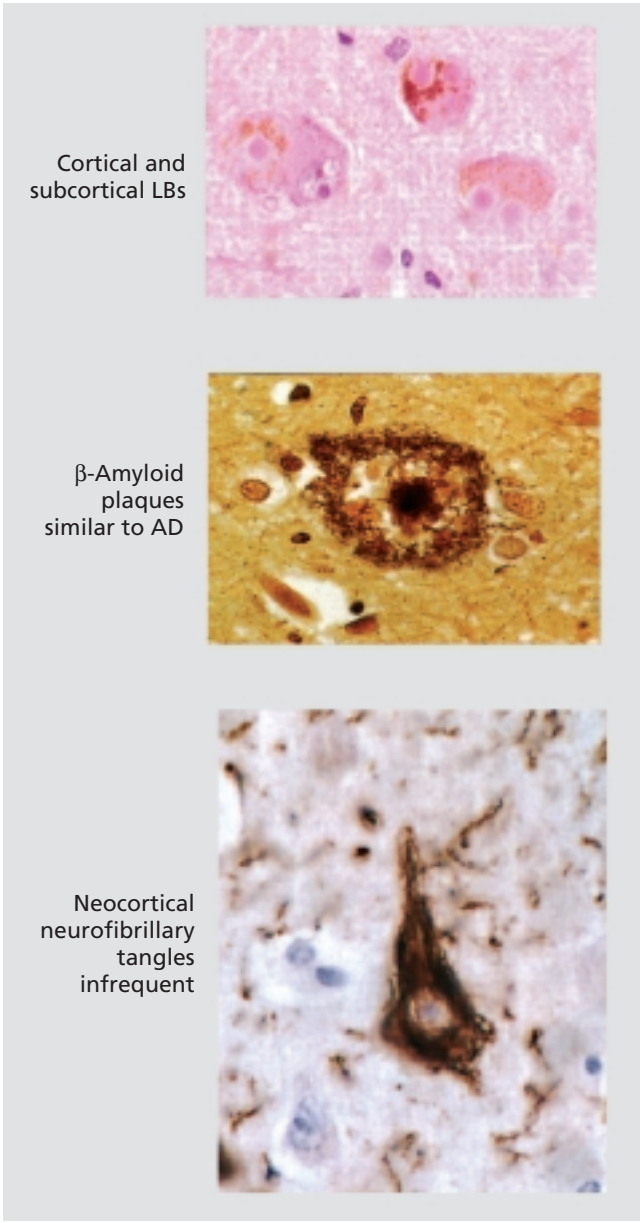

Figure 1. The neuropathology of dementia with Lewy bodies (DLB). LBs, Lewy bodies; AD, Alzheimer's disease.

DLB and Parkinson's disease dementia

The clinical and pathological classification of DLB is further complicated by its relationship with idiopathic Parkinson's disease, a disorder in which dementia may develop in up to 78% patients[20] and which is similar to DLB[21,22] in respect of fluctuating neuropsychological function,[23] neuropsychiatric features,[24] and extrapyramidal motor features *(Table I)*.[25]

There is considerable debate as to the relationship between the two diagnoses.[26] An arbitrary "1-year rule" is frequently used to "separate" them by proposing that onset of dementia within 12 months of parkinsonism qualifies as DLB and more than 12 months of parkinsonism before dementia qualifies as Parkinson's disease dementia (PDD). This is certainly helpful in individual clinical case diagnosis and management, but is increasingly hard to justify from a neurobiological point of view. There do

Cognitive profile
Fluctuating cognition
Extrapyramidal features
Neuropsychiatric symptoms
Lewy body distribution and density
Cholinergic and dopaminergic deficits
Neuroleptic sensitivity
Response to cholinesterase inhibitors

Table I. Similarities between dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD).

not seem to be major neuropathological differences between DLB and PDD, and it is not possible to make a confident retrospective clinical diagnosis based on autopsy findings alone. A Task Force of the Movement Disorders Society is presently addressing the issues of PD dementia, and its recommendations should help to clarify this complex and currently problematic area.

Clinical criteria for DLB

The core clinical features of DLB, as defined by consensus criteria *(Table II)*,[27] are fluctuating cognitive impairment, recurrent visual hallucinations, and parkinsonism. The specificity of a clinical diagnosis of "probable DLB" (two or more core features present) is high at >80%, but sensitivity is generally limited to around 50%.[28] The use of the more lenient "possible DLB" criteria, which require the presence of only one core feature, increases case detection rates at the cost of reduced diagnostic accuracy and may be useful in clinical practice for screening purposes.[29]

Clinical presentation and course of DLB

In general terms, the onset of DLB tends to be insidious, although reports of a period of increased confusion, the onset of hallucinations, or a significant fall may give the impression of a sudden onset. The main differential diagnoses of DLB are AD, vascular dementia, PDD, atypical parkinsonian syndromes, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD), and also Creutzfeld-Jakob disease (CJD).[27] The course of DLB is progressive, with cognitive test scores declining about 10% per annum, similar to AD.[30] Cognitive fluctuations may contribute to large variability in repeated test scores, eg, five Mini-Mental State Examination (MMSE) points difference over the course of a few days or weeks,[31] making it difficult to be sure of the severity of cognitive impairment by single examination. Survival times from onset until death are similar to AD,[32] although a minority of DLB patients have a very rapid disease course.[33,34]

The clinical diagnosis of DLB rests on obtaining a detailed history of symptoms from the patient and an informant, mental state examination, appropriate cognitive testing, and neurological examination. Systemic and pharmacological causes of delirium need to be excluded. There are as yet no clinically applicable electrophysiological, genotypic, or cerebrospinal fluid (CSF) markers to support a DLB diagnosis,[7] but neuroimaging investigations may be helpful in supporting the clinical diagnosis. Changes associated with DLB include preservation of hippocampal and medial temporal lobe volume on

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 and of frontal-subcortical skills and visuospatial ability may be especially prominent
Core features (two core features essential for a diagnosis of probable DLB, 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
Supportive features
• Repeated falls
• Syncope
• Transient loss of consciousness
• Neuroleptic sensitivity
• Systematized delusions
• Hallucinations in other modalities
• Rapid-eye movement (REM) sleep behavior disorder
• Depression
Features less likely to be present
• History of stroke
• Any other physical illness or brain disorder sufficient enough to interfere with cognitive performance

Table II. Consensus guidelines for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB).[27]

magnetic resonance imaging (MRI)[35,36] and occipital hypoperfusion on single-photon emission computed tomography (SPECT).[37,38] Other features, such as generalized atrophy,[36] white matter changes,[39] and rates of progression of whole brain atrophy,[40] appear to be unhelpful in differential diagnosis. Dopamine transporter loss in the caudate and putamen, a marker of nigrostriatal degeneration can be detected by dopaminergic SPECT and, in preliminary studies, has shown specificity and sensitivity of 85% or higher, and may be particularly helpful.[41,42]

Fluctuating cognition

The profile of neuropsychological impairments in patients with DLB differs from that of AD and other dementia syndromes,[43] reflecting the combined involvement of cortical and subcortical pathways and relative sparing of the hippocampus. Patients with DLB perform better than AD on tests of verbal memory,[44] but worse on visuospatial performance tasks[45] and tests of attention.[46] Fluctuations in cognitive function, which may vary over minutes, hours, or days, occur in 50% to 75% of patients, and are associated with shifting levels of attention and alertness. The assessment of fluctuating cognitive impairment poses considerable difficulty to most clinicians and has been repeatedly cited as a reason for low clinical ascertainment of DLB.[31,47] Newly proposed methods of assessment may be particularly helpful in this regard. These include caregiver- and observer-rated scales.[48] Questions such as whether there are episodes when the patient's thinking seems quite clear and then becomes muddled may be useful probes,[49,50] although one recent study[51] found carers' reports of fluctuation to be less reliable predictors of DLB diagnosis than more objective questions about daytime sleepiness, episodes of staring blankly, or incoherent speech *(Table III)*. Recording variation in attentional performance using a computer-based test system[52] offers an independent method of measuring fluctuation, which is also sensitive to drug treatment effects.[53]

Neuropsychiatric features

Although the expression "noncognitive features of dementia" is frequently used to describe a multiplicity of symptoms such as apathy, anxiety, delusions, hallucinations, and depression that are common in dementia, this term implies, probably incorrectly, that such features are independent of cognitive dysfunction. "Neuropsychiatric features"[54] is a more useful epithet to describe such symptoms, which are particularly common in DLB and which often prompt referral for clinical assessment.

Visual hallucinations are the most characteristic neuropsychiatric feature of DLB, and it is their persistence[55] that helps distinguish them from the episodic perceptual disturbances that occur transiently in dementias of other etiology or during a delirium provoked by an external cause. They are present in 33% of DLB cases at the time of presentation (range 11%-64%) and occur at some point during the course of the illness in 46% (13%-80%).[56] Well-formed, detailed, and animate figures are experienced, provoking emotional responses varying through fear, amusement, or indifference, usually with some insight into the unreality of the episode once it is over. It has been suggested that repeated visual hallucinations and associated visual phenomena in DLB are underpinned by disturbances in a lateral frontal cortex–ventral visual stream system,[57] emphasizing the cognitive basis of such symptoms. Visual hallucinations in DLB are associated with greater deficits in cortical acetylcholine[58] and predict better response to cholinesterase inhibitors.[59]

Ferman et al[51]	**Bradshaw et al[50]**
• Most carers report fluctuations	• Most carers report fluctuations
• DLB patients 87%; AD patients 73%	• DLB patients 77%; AD patients 67%
Four items distinguish DLB and AD • Daytime drowsiness and lethargy • Daytime sleep >2 h • Staring into space for long periods • Episodes of disorganized speech 3 or 4 features in 63% DLB patients, 12% AD patients, and 0.5% controls	Qualitative differences distinguish between fluctuations in DLB and AD Examples of "worst and best period of function" discriminated DLB patients 89% correct; AD patients 4% correct

Table III. Assessing cognitive fluctuation in dementia with Lewy bodies (DLB). AD, Alzheimer's disease.

Motor parkinsonism

Extrapyramidal signs (EPS) are reported in 25% to 50% of DLB cases at diagnosis, and 75% to 80% of patients develop some EPS during the natural course. The profile of EPS in DLB is generally similar to that in age-matched nondemented PD patients[25] with greater postural instability and facial impassivity, but less tremor.[60] Rate of motor deterioration is about 10% per annum, similar to PD,[61] but levodopa responsiveness is reduced, possibly due to additional intrinsic striatal pathology and dysfunction.[62]

Supportive features

Repeated falls, syncope, and transient losses of consciousness

Dementia of any etiology is probably a risk factor for all three of these clinical features and it can be difficult to clearly distinguish between them. Repeated falls may be due to posture, gait, and balance difficulties, particularly in patients with parkinsonism. Reported fall rates are 28% at the time of presentation (range 10%-38%) and 37% (22%-50%) at some point during the illness.[56] Syncopal attacks in DLB with complete loss of consciousness and muscle tone may represent the extension of LB-associated pathology to involve the brain stem and autonomic nervous system, leading to orthostatic hypotension and/or carotid sinus hypersensitivity, which are more common in DLB than AD or age-matched controls.[63] The associated phenomenon of transient episodes of unresponsiveness without loss of muscle tone may represent one extreme of fluctuating attention and cognition.

Neuroleptic sensitivity

The hypothesis, first made by the Newcastle group, of an abnormal sensitivity to adverse effects of neuroleptic medication was based upon two sets of independent observations. In the first, 67% (14/21) DLB patients received neuroleptics and 57% (8/14) deteriorated rapidly after either receiving them for the first time, or following a dose increase.[44] Mean survival time for these 8 patients was reduced to 7.4 months, significantly less than for the 6 patients who had only mild to no adverse reaction (28.5 months) and the 7 never receiving neuroleptics (17.8 months). In the second study, 54% (7/16) neuroleptic-treated DLB patients had neuroleptic sensitivity reactions and their mortality risk, estimated by survival analysis, was increased by a factor of 2.7.[4] Newer atypical antipsychotics used at low dose may be safer in this regard, but sensitivity reactions have been documented with most and they should be used with great caution.[7]

Other clinical features

Delusions are common in DLB, in 56% at the time of presentation and 65% at some point during the illness. They are usually based on recollections of hallucinations and perceptual disturbances and consequently often have a fixed, complex, and bizarre content that contrasts with the mundane and often poorly formed persecutory ideas encountered in AD patients, which are based on forgetfulness and confabulation.

Auditory hallucinations occur in 19% (range 13%-30%) at presentation and 19% (13%-45%) at any point. Together with olfactory and tactile hallucinations, these may be important features in some DLB cases and can lead to initial diagnoses of late-onset psychosis[64] and temporal lobe epilepsy.[44]

Sleep disorders have more recently been recognized as common in DLB with daytime somnolence and nocturnal restlessness,[65] sometimes as prodromal features. Rapid-eye movement (REM) sleep-wakefulness dissociations may explain several features of DLB that are characteristic of narcolepsy (REM sleep behavior disorder, daytime hypersomnolence, visual hallucinations, and cataplexy).[66] Sleep disorders may contribute to the fluctuations typical of DLB and their treatment may improve fluctuations and quality of life.[66] Early urinary incontinence has been reported in DLB compared with AD,[67] reflecting involvement of autonomic systems. Depressive symptoms are reported in 33% to 50% of DLB cases, a rate higher than in AD and similar to PD,[68] and may be related to involvement of monoaminergic brain-stem nuclei.

Management of DLB

General considerations

When dealing with the management of DLB or PDD patient, it is helpful first to draw up a problem list of cognitive, psychiatric, and motor disabilities, and to then ask the patient and carer to identify the symptoms that they

find most disabling or distressing and which carry highest priority for treatment.[69] The clinician should explain, before any drugs are prescribed, that treatment gains in target symptoms may be associated with worsening of symptoms in other domains. The specific risks of neuroleptic sensitivity reactions (see above) should be mentioned in all cases and it is prudent to mark patient case notes and records with an alert to reduce possibility of inadvertent neuroleptic prescribing, particularly in primary care or emergency room settings.

Nonpharmacological strategies for cognitive symptoms, including explanation, education, reassurance, orientation and memory prompts, attentional cues, and targeted behavioral interventions, are an integral part of the management of DLB, and pharmacological treatment is most successful when prescribed as part of a comprehensive management approach. Similarly, if a patient with DLB has become acutely confused and psychotic, intercurrent infection and subdural hematoma, in particular, should be actively excluded. It cannot always be assumed that worsening of symptoms is simply part of the natural fluctuating history of DLB.

Specific treatments

The effectiveness of levodopa on motor symptoms in DLB is thought to be less than in uncomplicated PD, though trial data are lacking. Treatment refractoriness may be related to intrinsic striatal degeneration in DLB and PDD.[70] The clinician should aim for the lowest effective dose of levodopa monotherapy,[71] since higher doses or other antiparkinsonian agents, are likely to be associated with increased confusion and hallucinations.

Evidence is accumulating that cholinesterase inhibitor (ChEI) drugs are effective and relatively safe in the treatment of neuropsychiatric and cognitive symptoms in DLB and PDD, but the number of patients studied is relatively small and larger trials are still needed. In addition to the usual gastrointestinal side effects associated with this class of drug, increased cholinergic activity in DLB patients may cause hypersalivation, rhinorrhea, and lacrimation,[72] and exacerbate postural hypotension and falls.[73] Improvements are generally reported as greater than those achieved in AD *(Figure 2)*.[74,75]

Apathy, anxiety, impaired attention, hallucinations, delusions, sleep disturbance, and cognitive changes are the most frequently cited treatment-responsive symptoms in DLB patients treated with ChEIs.[3,76,77]

These responses are consistent with the loss of basal forebrain and pedunculopontine cholinergic projection neurones and the associated neocortical cholinergic deficits[58] that have been identified in DLB. Reduction in temporal choline acetyltransferase (ChAT) is more extensive in those DLB patients with hallucinations than in those without,[78] and increased muscarinic receptor density, which probably occurs in response to the marked presynaptic cholinergic deficits, is particularly pronounced in DLB patients with delusions compared with those without.[79] DLB patients with visual hallucinations were recently reported to experience greater improvements in performance of attentional tasks following ChEI administration compared with nonhallucinators.[59] There are only limited open-label data available of long-term treatment effects,[80] which do seem to be sustained, with symptomatic deterioration (sometimes rapid) when treatment is withdrawn.[81]

Conclusion

As our understanding of the pathological processes underpinning neurodegenerative disorders becomes greater, we might hope that clinical classification and detection of subtypes would become more precise. The example of DLB suggests that this may not be so straightforward. The majority of cases of dementia in

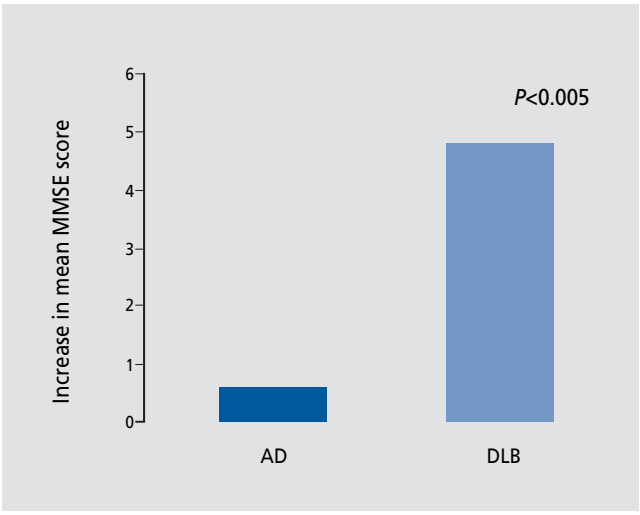

Figure 2. Cholinesterase inhibitors in dementia with Lewy bodies (DLB). Twelve Alzheimer's disease (AD) patients and four DLB patients were treated with donepezil 5 mg/day for 6 months. Nonsignificant difference in changes on BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease Rating Scale). MMSE, Mini-Mental State Examination.[74]

older people appear to be related to multiple and overlapping pathologies and this is reflected in considerable clinical heterogeneity. Clinical syndromes such as "probable" DLB or AD are useful predictors of the predominant underlying disease process and are of particular use in planning treatment approaches. The new challenge is to devise better methods of determining the atypical and mixed pathology cases with greater accuracy, acknowledging the existence of clinical and biological overlap.[82] ❑

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Demencia con cuerpos de Lewy

La demencia con cuerpos de Lewy (DCL) es la segunda causa más común de demencia neurodegenerativa en las personas de edad avanzada y representa el 10% a 15% de todos los casos. Ocupa parte de un espectro que incluye la enfermedad de Parkinson y la insuficiencia autonómica primaria. Todas estas enfermedades comparten una patología neural que se basa en una agregación anormal de la proteína sináptica α-sinucleína. Es importante identificar pacientes con DCL con precisión ya que ellos tienen síntomas específicos, deterioros y discapacidades funcionales que difieren de otros síndromes comunes de demencia como la enfermedad de Alzheimer, el deterioro cognitivo vascular y la demencia frontotemporal. Se han validado criterios diagnósticos clínicos para la DCL mediante la autopsia, pero fallan en la detección de una minoría no despreciable de casos con presentaciones atípicas que a menudo se deben a la presencia de patología mixta. Los pacientes con DCL tienen frecuentemente graves reacciones de sensibilidad a los neurolépticos, las que están asociadas con un aumento significativo de la morbilidad y de la mortalidad. El tratamiento con inhibidores de la colinesterasa en general es bien tolerado y mejora significativamente los síntomas cognitivos y neuropsiquiátricos. Aunque virtualmente la DCL no se reconocía hace 20 años, dentro de esta década podría llegar a ser uno de los trastornos neurodegenerativos más tratables de la vejez.

La démence à corps de Lewy

La démence à corps de Lewy (DCL) représente la deuxième cause la plus fréquente des démences neurodégénératives chez les sujets âgés, soit 10 à 15 % de l'ensemble des cas. Elle appartient à un éventail qui va de la maladie de Parkinson à la déficience autonome primaire. Toutes ces maladies partagent une pathologie neuronale basée sur une agrégation anormale de la protéine synaptique α-synucléine. Il est important d'identifier avec précision les patients atteints de DCL car leurs symptômes, déficits ou incapacités fonctionnelles sont spécifiques et diffèrent des autres syndromes démentiels courants comme la maladie d'Alzheimer, le déficit vasculaire cognitif et la démence frontotemporale. Les critères diagnostiques cliniques pour la DCL ont été validés par autopsie mais une minorité non négligeable n'est pas détectée, il s'agit de cas atypiques dont la pathologie est souvent mixte. Les patients atteints de DCL ont souvent une hypersensibilité sévère aux neuroleptiques, associée à une morbidité et une mortalité significativement accrues. Le traitement par anticholinestérasiques est habituellement bien toléré et améliore considérablement les symptômes cognitifs et neuropsychiatriques. Bien que pratiquement méconnue il y a 20 ans, la DCL pourrait devenir au cours des 10 ans à venir l'une des maladies neurodégénératives de survenue tardive les plus accessibles au traitement.

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