The Dementia with Lewy Bodies

Subjects: Neurosciences

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Dementia with Lewy Bodies (DLB) is a common form of cognitive neurodegenerative disease. Only one third of patients are correctly diagnosed due to the clinical similarity mainly with Alzheimer's disease (AD).

Keywords: dementia with lewy bodies ; Alzheimer's disease ; cerebro-spinal fluid ; MRI ; FP-CIT ; MIBG ; cognitive ; hallucinations ; RBD ; fluctuations

1. Epidemiology of DLB

Dementia with Lewy bodies (DLB) is the main neurodegenerative pathology affecting cognitive functions in the elderly after Alzheimer's disease (AD) [1]. It begins after the age of 50 and represents 20% of demented patients [2]. First described in 1961 [3], it is only recently that it has been recognized as a common cause of dementia [4].

2. Diagnosis Criteria

DLB diagnosis criteria have evolved over time and were revised in 2005 and again in 2017 [5][6]. The McKeith criteria for the diagnosis of probable DLB are, in addition to cognitive decline (essential criterion), at least two core criteria and for the possible diagnosis either a core criterion with or without suggestive criteria, or at least one suggestive criterion (**Table 1**). McKeith and the international DLB consortium have also defined diagnosis criteria for prodromal forms [7]. The prodromal stage of DLB (pro-DLB), also called mild cognitive impairment due to Lewy bodies has been described in detail: the first criteria of this prodromal stage are similar to the stage of dementia with the difference that a decrease in functional capacity is either non-existent or minimal. So pro-DLB can be defined as the presence of the disease but cognitive impairment is not sufficient to lead to functional deficits in activities of daily living, and thus to dementia. Descriptions of pro-DLB criteria have been proposed [8]: pro-DLB can be defined as those patients who meet the revised diagnostic criteria for DLB but instead of dementia, fit the criteria for mild cognitive impairment (MCI) [7].

Table 1. Diagnosis criteria of DLB.

Clinical Characteristics	
Essential Criterion	
Cognitive decline of sufficient severity to interfere with activities of daily living. The deficits frequently concern attentional, executive and visuospatial abilities.	
Core Criteria	**Supportive Criteria**

Clinical Characteristics	
Essential Criterion	
	➢ Severe sensitivity to antipsychotics ➢ Postural instability ➢ Repeated falls ➢ syncope or other transient episodes of unresponsiveness ➢ Severe autonomic dysfunction: constipation, orthostatic hypotension, urinary incontinence ➢ Hallucinations in other sensory modalities (ex: auditory hallucination) ➢ hypersomnia ➢ hyposmia ➢ Systematized delirium: delirium where the delusional ideas are organized, giving the impression of coherence ➢ Apathy, anxiety, depression
➢ Cognitive fluctuations with significant changes in attention and alertness ➢ Recurrent visual hallucinations that are typically well formed and detailed ➢ REM sleep behavior disorder, which may precede cognitive decline ➢ One or more characteristics of parkinsonian syndrome: bradykinesia, rest tremor, rigidity	
Biomarkers	
Indicative	**Supportive**
➢ Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT (FP-CIT=DAT-scan) or PET (Fluorodopa) ➢ Abnormal (low uptake) 123Iodine-MIBG myocardiac scintigraphy ➢ Polysomnographic confirmation of REM sleep without atonia	➢ MRI, CT-scan: relative preservation of medial temporal lobe structures (unlike AD patients) ➢ Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET imaging ➢ EEG: Prominent posterior slow-wave activity with periodic fluctuations in the pre-α/θ range

Core criteria: the presence of two of the symptoms listed are essential for the probable diagnosis, and the presence of only one of them for the possible diagnosis of DLB. Suggestive criteria (green headband) can lead to a diagnosis of probable DLB (presence of at least one core criterion, and one of these suggestive criteria), or possible DLB (presence of at least one of these criteria without core criteria).EEG: Electroencephalography; FDG: Fluorodeoxyglucose (18F); MRI: Magnetic Resonance Imaging; PET scan: positron emission tomography; REM: rapid eye movement; SPECT: Single photon emission computed tomography; 123 Iodine-MIBG: 123 iodine-metaiodobenzylguanidine adapted from [6].

3. Differential Diagnosis with AD and PD

Due to some clinical and neuropsychological similarities with AD, the diagnosis of DLB is not straightforward. The main confounding pathologies are AD, vascular dementia, Parkinson's disease dementia (PDD), frontotemporal lobe degeneration (FTLD), progressive supranuclear palsy (PSP), multisystem atrophy (MSA), corticobasal degeneration (CBD) and prion diseases for brain diseases and recurrent depression, schizophrenia, bipolar disorders for psychiatric diseases. The most common differential diagnosis for the clinician remains with AD.

DLB is close to Parkinson's disease (PD) due to the presence of Parkinsonism (bradykinesia, rigidity, postural instability and resting tremor), which is often discrete, especially at the beginning of the disease [7][8]. DLB is also close to PD because of its pathophysiology, with the presence of positive α-synuclein (α-syn) aggregates in the brain, forming Lewy bodies [9]. Thus, PD and DLB, due to common aggregation processes, form a set of pathologies called synucleinopathies,

including also PDD and multiple system atrophy (MSA). The pathophysiological difference that can be noted between DLB and PD is the aggregates localization. While α-syn aggregates are mostly localized in the brainstem and in the substantia nigra at the beginning of PD, they are rather diffuse throughout the brain in the early stages of DLB. Moreover, the three-dimensional structure of α-syn is different from the two others synucleinopathies: PD and MSA [10]. The differential diagnosis between PDD and DLB depends on the timing of events between the cognitive and motor impairment. In PDD, the cognitive symptoms appear after the parkinsonian syndrome, whereas in DLB the motor deficits appear after the cognitive deficits. Thus, according to an arbitrary rule, if the cognitive deficits appear at least one year after the motor deficits it will be PDD, otherwise it will be DLB [4][6].

Many symptoms of DLB are close to those of AD, especially at the onset of the pathology: executive functions, visual memory, visuo-constructive and visuospatial abilities with weaknesses for episodic memory, short-term and working memory, verbal initiation, praxis, language, as well as social cognition [11]. DLB and AD can often be associated: 87% of DLB patients have moderate to abundant cortical amyloid plaques [12]. Thus, in these patients with AD/DLB diseases, DLB being masked, this disease is more difficult to diagnose.

DLB presents certain clinical specificities such as visual illusions or hallucinations and fluctuations in attention, but also a particular sensitivity to neuroleptics [5][8]. Despite the very high diagnosis specificity of these criteria (the specificity of probable DLB is 95.1% in early stages and 88% in late stages) [4][13], their sensitivity remains low (32%) in pure DLB or even lower (12%) when associated with AD [14]. In other words, DLB is still a largely underdiagnosed disease in more than two-thirds of cases. It is therefore essential to discover new biomarkers that can distinguish DLB from AD to improve differential diagnosis.

4. Therapeutic Management

The treatment of DLB patients consists of a combination of pharmacological and non-pharmacological treatments. At the pharmacological level, each symptom has its own symptomatic treatment: donepezil or rivastigmine for cognitive disorders and cognitive fluctuations, levodopa in small doses for Parkinsonism, melatonin for behavioral disorders in REM sleep behavior disorders (RBD), clozapine, quetiapine and pimavanserine for invasive hallucinations or delusion [15]. Other antipsychotics are contraindicated because they are poorly tolerated: There is a risk of increased cognitive impairment, falls, increased parkinsonian syndrome, confusion, neuroleptic malignant syndrome and even death [16]. On a non-pharmacological level, cognitive remediation is used to combat cognitive disorders, and physical therapy to combat motor disorders and falls.

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