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Lewy Body Dementia: A Review

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Abstract

Lewy Body Dementia (LBD) is a frequent and complex neurodegenerative pathology, shorter in duration than Alzheimer's disease. Many advances have been made both pathophysiologically and imaging, allowing earlier diagnosis. Although there are few double-blind clinical studies on drug therapies, the place of anticholinesterase inhibitors, L-dopa and new antipsychotics is slowly emerging.

Introduction

Lewy body dementia (LBD) is the second most common neurodegenerative dementia after Alzheimer's disease. It is a complex disease that borrows certain symptoms to Alzheimer's disease and Parkinson's disease, so difficult to recognize or diagnose [1]. Lewy body dementia also called Lewy body disease is a form of cognitive disorder characterized by abnormal deposits of a protein called alpha-synuclein that form inside brain cells. Unfortunately, there are very few epidemiological studies available. According to the studies, the prevalence of LBD varies from 0 to 5% in the general population and from 0 to 30.5% in all cases of dementia combined. The incidence would be 0.1% per year for the general population and 3.2% per year for all new cases of dementia [2]. LBD mainly affects parts of the brain related to cognitive functions and movement. The term dementia describes a state of degradation of the intellectual faculties which eventually leads to a loss of autonomy. On some points, Lewy body dementia is approaching Alzheimer's disease or Parkinson's disease. It is distinguished by a generally more rapid development and marked deterioration of the mental faculties. Like other neurodegenerative dementias, it affects mainly the elderly.

What is a Lewy body?

The bodies of Lewy bear their name in honor of Dr. Friederich Heinrich Lewy who was the first to describe these structures that he had discovered in the brains of patients who at the time of their deaths suffered from Parkinson's disease. Lewy bodies are neuronal inclusions, usually spherical. They are mainly composed of neuronal filaments and a protein called alpha-synuclein, a presynaptic protein that has a role in learning. The abnormal accumulation of this protein inside the nerve cells of the brain, in the form of aggregates of insoluble filaments, leads to the formation of deposits which interrupt the messages transmitted by the brain [3]. In patients with Parkinson's disease, Lewy bodies are found in cells located in the brain stem (at the base of the brain) and play a role in controlling movement. In the LBD, Lewy bodies are also present in the outer layer of the brain called the cortex which is responsible for mental functions. These "cortical Lewy bodies" constitute the essential pathological element of Lewy body dementia.

Diagnosis of Lewy body dementia

Clinical and para-clinical criteria that are strongly suggestive of LBD, i.e., are significantly more common than in other dementia and less specific complementary criteria. The existence of an evolving cognitive disorder is a necessary condition for diagnosing LBD even though it is not the only element. The cognitive profile includes both cortical and subcortical impairments associated with significant attentional deficits and marked visual-spatial and executive dysfunction [4]. Patients with LBD can be differentiated from those with Alzheimer's disease because of the relative preservation of recognition and greater impairment of verbal fluency, visual perception, and performance tasks. Some patients may, however, have more marked memory deficits, suggestive of Alzheimer's disease. The MMS does not distinguish between LBD and other dementia, some patients with normal scores.

Most patients with Parkinson's disease develop dementia within 10 years or more after the onset of motor disorders. With the exception of age of onset, time course and possible response to L-dopa, several studies show that there are no major differences between LBD and parkinsonian dementia with respect to cognitive profile, performance neuro-psychiatric disorders, sleep disorders, dysautonomia, the type and severity of Parkinsonism, sensitivity to neuroleptics and the response to anticholinesterase agents [5].

Some authors consider these clinical presentations as different elements belonging to

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the common spectrum of a larger entity, Lewy Body Disease. This unitary approach seems preferable for genetic and molecular studies as well as for the development of treatments. LBD is suspected when dementia precedes or appears at the same time as Parkinsonism and parkinsonian dementia when dementia occurs in a well-established Parkinson's disease setting. There are three main characteristics essential to the diagnosis of LBD: fluctuation of cognitive disorders, visual hallucinations and Parkinsonism [6]. Fluctuations are difficult to evaluate by a simple question like "Does the patient have moments of lucidity and moments of confusion?" Since two recent studies have shown that 75% of caregivers of an Alzheimer's patient or having an LBD answer yes! It is therefore recommended to use scales such as the Clinician Assessment of Fluctuation Scale, the Semi-structured One Day Fluctuation Assessment Scale or the Mayo Fluctuations Composite Scale. Visual hallucinations are complex and recurrent [7,8].

They are usually early but underestimated by caregivers and are one of the most useful signs for clinical diagnosis. The NPI (Neuropsychiatric Inventory) makes it possible to evaluate their frequency and intensity and to differentiate them from other types of hallucinations [9].

Patients with hallucinations have more marked visual-perceptual dysfunction. A high number of Lewy bodies in the anterior temporal lobe, lower lobe and amygdala are found in these patients at autopsy [10]. These areas are involved in the genesis of complex visual images. Functional imaging shows a decrease in perfusion of regions corresponding to the visual cortex. Visual hallucinations are associated with a greater deficit in cortical acetylcholine and their existence predicts a better response to anticholinesterase inhibitors.

The severity of the extra-pyramidal syndrome is identical in LBD and Parkinson's disease with or without dementia. Nevertheless, there is an axial predominance with greater postural instability, walking and a clearer amimia. Tremor rest is less common. A scale like the Unified Parkinson Disease Rating Scale (UPDRS) may be useful in an LBD to evaluate motor syndrome [11]. The response to L-dopa is less in LBD than in uncomplicated Parkinson's disease, probably because of intrinsic striatal degeneration and because most Parkinsonian symptoms are not dopaminergic [12]. However 75% of the patients are still improved by this treatment.

There are criteria suggestive of LBD such as the existence of paradoxical sleep disorders, increased sensitivity to neuroleptics and a decrease in the dopamine transporter to functional imaging [13]. If one or more of the evocative characteristics are present and associated with one or more major criteria, then the diagnosis of LBD should be made. A possible LBD may be suspected if one or more of these evocative criteria exist in a demented patient even in the absence of primary criteria. REM (Rapid Eye Movement). REM sleep disorders manifest themselves in often colorful and frightening dreams without muscular atony. Patients "live" their dreams with screams, leg movements and significant agitation. Spouses report the existence of these disorders long before the onset of Parkinsonism or dementia. They are frequently associated with underlying alpha-synucleinopathy such as LBD, Parkinson's disease or multi-systemic atrophy and rarely present in other neurodegenerative disorders. REM sleep disorders and daytime sleepiness also contribute to cognitive fluctuations. It is essential to ask the patient and his entourage about the existence of such disorders with a sleep questionnaire if necessary. The diagnosis can be confirmed by polysomnography.

The increased sensitivity to neuroleptics is strongly suggestive of an LBD but its absence does not exclude the diagnosis since 50% of patients who receive neuroleptics, atypical or not, do not have intolerance [14]. Functional imaging of the dopamine transporter defines the integrity of the nigrostriatal dopaminergic system and has a diagnostic implication in the face of a tremor of uncertain etiology. The density of the transporter is abnormal in idiopathic Parkinson's disease, multi-systemic atrophy and supra-nuclear paralysis. Low striatal dopaminergic activity is also seen in the LBD but the images are normal in Alzheimer's disease. Functional imaging

can therefore be useful for distinguishing the two pathologies. Finally, we observe additional criteria often present in the LBD but not specific. Severe autonomic dysfunction may be seen early in the disease with orthostatic hypotension, neurovegetative cardiovascular instability, urinary incontinence, constipation, asthenia, and swallowing disorders. This attack is often responsible for repeated falls, fainting and brief fainting. Patients sometimes have hallucinations of other types, a depressive syndrome or systematized delirium that may misdiagnosis, at the initial stage, to a psychiatric pathology. The differential diagnosis normally excludes other systemic or neurological pathologies, but at necropsy, white matter involvement, microcirculation or the presence of deficiencies are observed in 30% of patients with LBD. The various manifestations of the symptoms are directly related to the distribution of Lewy bodies. Thus, when they are in the hippocampus region, memory disorders are observed; if they are located in the associative visual areas of the posterior part of the temporal lobe, the patients are victims of hallucinations; if the Lewy bodies are concentrated in the right parietal region responsible for spatial analysis, patients have difficulty orienting.

Additional tests

There are several complementary tests that help with the diagnosis. For the moment, there is no clinical application of the different cellular markers. Medial temporal hippocampal and temporal lobe preservation, putamen atrophy, and SPECT occipital hypoperfusion were observed, PET hypometabolism without MRI occipital atrophy. On the other hand, the degree of global atrophy of the brain, the progression of the latter and the severity of white matter disorders do not help the diagnosis. Meta iodobenzyl guanidine scintigraphy (MIBG), which quantifies the degree of sympathetic cardiac innervation, is decreased in the LBD. This would be a highly sensitive and specific examination in the differential diagnosis between Alzheimer's disease and an LBD [15]. The standard electroencephalogram may show early deceleration with wave bursts in the temporal and frontal territories. At the anatomopathological level, Lewy bodies correspond to visible alpha-synuclein aggregates using immunohistochemically and semi-quantitative methods to calculate the density of lesions and to grade the severity of autopsy involvement. It seems that cerebral localization is more important than the amount of Lewy body.

Is there a treatment for Lewy body dementia?

At present, there are no specific treatments for this neurodegenerative disorder [16]. The treatment of Lewy body is symptomatic, i.e. it is limited to managing symptoms, particularly hallucinations, extra pyramidal syndrome, and cognitive impairment. LBD is therefore a frequent and complex neurodegenerative disorder with a shorter evolution than Alzheimer's disease. Many advances have been made in pathophysiology and imaging, leading to future diagnosis. Although there are few double-blind clinical studies on drug therapy, the role of anticholinesterase drugs, L-dopa and new antipsychotics is emerging but there is a lack of research on dementia with Lewy bodies.

Management is based on the detection and early diagnosis of the disease associated with the treatment of the various symptoms through drug therapies and orthophonic, physiotherapy and psychotherapeutic support. L-dopa can be used in Parkinson's disease of LBD and in Parkinson's dementia, low dose and gradually increasing to the minimum effective dose to avoid side effects. Anticholinergics are prohibited. Visual hallucinations often associated with delirium, anxiety, and behavioral disturbances, can be treated with anticholinesterase drugs. They have an antipsychotic effect in DCL but not in the context of Alzheimer's disease. While open-label studies have demonstrated their beneficial effect, only rivastigmine has shown efficacy versus placebo. Hallucinations regress when attention disorders are improved. In addition to the classic digestive side effects of these compounds, there is hyper salivation, lacrimation and bladder instability or an exacerbation of the extra-pyramidal syndrome. If these medications have little or no

effect, atypical neuroleptics (quetiapine, clozapine, aripiprazole) may be prescribed by warning the patient and their caregiver of the risk of hypersensitivity [17].

In case of depression, selective or non-selective serotonin reuptake inhibitors are effective. Tricyclic antidepressants with anticholinergic effects are not recommended. In case of sleep disturbances, some use clonazepam 0.25 mg, melatonin 3 mg or quetiapine 12.5 mg at bedtime, with a gradual adjustment. Anticholinesterase inhibitors also act on apathy and sleep disorders. They can be beneficial on cognitive fluctuations with an impact on the overall functioning and activities of daily living. Their effects would be greater than in Alzheimer's disease but we do not have long-term studies.

Conclusion

LBD is therefore a common and complex neuro-degenerative pathology, shorter in duration than Alzheimer's disease. Many advances have been made both pathophysiological and imaging, allowing earlier diagnosis. Although there are few double-blind clinical studies on drug therapies, the place of anticholinesterase inhibitors, L-dopa and new antipsychotics is slowly emerging.

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