

## Dementia with Lewy bodies and Parkinson's disease dementia-two independent disorders or one clinical entity within a clinical spectrum of synucleinopathies?

Otępienie z ciałami Lewy'ego i otępienie w przebiegu choroby Parkinsona-dwie niezależne choroby czy też jedna jednostka chorobowa w ramach spektrum klinicznego alfa-synukleinopatii?

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### Abstract

**Introduction:** Both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) are important dementia syndromes that overlap in their clinical features and clinical course, neuropathological abnormalities, and also therapeutic approach. Nevertheless it is still unclear whether DLB and PDD are two different disorders that require differentiation or are one clinical entity within a spectrum of Lewy body disease. Currently these disorders are mainly distinguished on the basis of the relative timing of the onset of symptoms of dementia and parkinsonism. The present paper presents current concepts on the pathogenesis of both disorders and their possible overlap.

**Material and methods:** Online databases in the field of DLB and PDD were searched for to find potentially eligible articles. Only most recent articles published after the year 2000 were chosen.

**Results:** The clinical features of DLB and PDD are similar and include dementia with hallucinations and cognitive fluctuations, as well as parkinsonian signs. Also cognitive deficits are similar in PDD and in DLB, with predominance of executive dysfunction, visual-spatial deficits and memory impairment. Neuropathological changes in both disorders involve the presence of Lewy bodies and Lewy neurites within brainstem, limbic and neocortex, as well as loss of midbrain dopamine cells, and loss of cholinergic neurons in the nuclei of ventral forebrain.

**Conclusions:** Similarities in clinical manifestation, neuropsychological deficits and neuropathological abnormalities may suggest that both DLB and PDD are two different phenotypes of the same disorder. This review article presents current knowledge on similarities and differences between these two clinical entities and raises the question whether they require differentiation or not.

**Keywords:** dementia with Lewy bodies, Lewy body disease, dementia, synucleinopathies

### Streszczenie

**Wstęp:** Zarówno otępienie z ciałami Lewy'ego (DLB), jak i otępienie w chorobie Parkinsona (PDD) są ważnymi jednostkami chorobowymi, które wykazują podobieństwo pod względem wielu objawów, przebiegu klinicznego, nieprawidłowości neuropatologicznych, a także podejścia terapeutycznego. Nie jest jasne, czy DLB i PDD to dwie różne jednostki chorobowe, które wymagają różnicowania, czy też stanowią jeden zespół chorobowy w spektrum klinicznego choroby z ciałami Lewy'ego. Obecnie zaburzenia te odróżnia się głównie na podstawie momentu pojawienia się objawów otępienia i parkinsonizmu względem siebie.

**Materiały i metoda:** Dokonano przeglądu internetowych baz danych w celu znalezienia najbardziej odpowiednich artykułów poświęconych DLB i PDD. W niniejszym artykule poglądowym wykorzystano najnowsze prace opublikowane po roku 2000.

**Dyskusja:** Cechy kliniczne DLB i PDD są podobne i obejmują otępienie z halucynacjami i wahaniami funkcji poznawczych, a także objawy parkinsonizmu. Również deficyty poznawcze są podobne w PDD i DLB, z przewagą dysfunkcji wykonawczych, deficytów wzrokowo-przestrzennych i upośledzenia pamięci. Zmiany neuropatologiczne w obu zaburzeniach obejmują obecność ciał Lewy'ego i neurytów Lewy'ego w pniu mózgu, limbice i korze nowej, a także utratę komórek dopaminowych śródmózgowia i

utratę neuronów cholinergiczných w jądrach przodomózgowia brzuszneę.

**Wnioski:** Podobieństwa w objawach klinicznych, deficytach neuropsychologicznych i nieprawidłowościach neuropatologicznych mogą sugerować, że zarówno DLB, jak i PDD są dwoma różnymi fenotypami tego samego zaburzenia. W artykule przeglądowym przedstawiono aktualny stan wiedzy na temat podobieństw i różnic między tymi dwoma jednostkami klinicznymi oraz postawiono pytanie, czy wymagają różnicowania, czy nie.

**Słowa kluczowe:** otępienie z ciałami Lewy'ego, ciała Lewy'ego, synukleinopatie

## Introduction

The complex relationship between dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) has been widely investigated and discussed in the literature [1-8].

At the beginning of the 20th century, Frederick Lewy first described the cytoplasmic inclusions currently known as Lewy bodies in the substantia nigra of Parkinson's disease (PD) patients [9]. Later, in the 1980s, due to availability of ubiquitin and  $\alpha$ -synuclein immunostaining, it turned out that Lewy bodies were a common neuropathologic finding in subjects with dementia. Now it is known, that Lewy body pathology can be seen in different neurodegenerative disorders, including dementia with Lewy bodies (DLB), idiopathic PD, multiple system atrophy (MSA) and dementia in the course of PD (Parkinson's disease dementia, PDD)

The clinical features of DLB and PDD are similar and include dementia with concomitant parkinsonian syndrome, hallucinations and cognitive fluctuations. The cognitive domains that are mostly impaired in DLB and PDD also overlap, with predominance of executive and visual-spatial problems, as well as memory impairment [10]. In DLB, dementia symptoms usually precede parkinsonian syndrome, but may also occur within 1 year from the onset of parkinsonian syndrome [11]. The diagnosis of PDD can be made, when cognitive impairment occurs after the diagnosis of PD has already been made [12].

Also neuropathological changes in both these disorders are similar and include the presence of Lewy bodies in the cortex and in the limbic system and Lewy neurites in the brainstem, limbic region and neocortex, and also loss of dopamine cells in the midbrain, and loss of cholinergic neurons in ventral forebrain nuclei [13, 14].

Additionally, neuritic plaques that contain amyloid depositions and neurofibrillary tangles can be found in both DLB patients and in PD patients. As pathology typical for Alzheimer's disease (AD) occurs also in Lewy body dementias, that is why current neuropathologic criteria for DLB weigh  $\alpha$ -synuclein pathology against AD neurofibrillary tangle pathology to estimate the

probability that Lewy body disease was the underlying reason for the clinical syndrome present in a living patient [15]. Interestingly, in Lewy body dementias on autopsy examination, it is not possible to differentiate between DLB and PDD. All the above mentioned similarities led to the concept that both PDD and DLB are one clinical entity within the spectrum of Lewy body dementias. In the present review we present differences and similarities of these two clinical entities and current concepts on its overlap.

## Epidemiology

The incidence of dementia with Lewy bodies (DLB) among people over 65 years of age is 0.5-1.6 / 1000 person-years. The disease accounts for 3.2-7.1% of all dementia cases [16]. PDD accounts for 3-4% of all dementias [17]. Its incidence increases with PD duration. The average time to onset of dementia from the diagnosis of PD is about 10 years [18, 19]. On average, after 20 years of PD duration, up to 83% of patients develop symptoms of dementia [20]. Each year, 10% of PD patients develop PDD [21].

## Neuropathological changes

Lewy bodies are the main, but not the only, histopathological finding in the central nervous system (CNS) of patients suffering from DLB and PDD [22]. The  $\alpha$ -synuclein that makes up Lewy bodies may promote deposition of  $\beta$ -amyloid and  $\tau$  protein [23]. Neuropathological changes characteristic of Alzheimer's disease are also common in DLB and in PDD [24]. It has been proven that  $\alpha$ -synuclein is responsible for damaging the mechanisms related to the release of synaptic vesicles [25], which leads to disturbances in the activity of dopaminergic [26] and cholinergic connections [14]. All the abnormalities mentioned above occur both in PDD and in DLB, however there are differences in their distribution and intensity within the central nervous system (CNS). The location where the most  $\alpha$ -synuclein accumulates in course of PDD is cingulate cortex [27], while in DLB it is hippocampus and amygdala [28, 29]. Abnormalities typical of AD are more severe in other locations such as: striatum, neocortex, claustrum, and entorhinal cortex in

the course of DLB [22].

Based on the PET scans imaging for  $\beta$ -amyloid depositions and the histopathological examinations showing the distribution of lesions in the CNS, it was hypothesized that a different pattern of the development of neuropathological changes may be responsible for the differences in clinical course between DLB and PDD. The early deposition of  $\beta$ -amyloid in the cortex to which  $\alpha$ -synuclein joins, is expected to be responsible for cognitive impairment in DLB. The course of PDD is less dependent on  $\beta$ -amyloid and to a greater extent on the passage of  $\alpha$ -synuclein from the brainstem to the cortex [4].

### Cognitive symptoms

In both these disorders dementia is an important syndrome, nevertheless in contrast to PDD, in DLB dementia with concomitant visual hallucinations occurs early in the course of the disease. The most important clue in the differential diagnosis between DLB and PDD is the difference between the time of onset of motor and dementia symptoms. In DLB dementia often precedes parkinsonism or occurs simultaneously with parkinsonian signs. In PDD dementia occurs months or years, after the diagnosis of PD has been made. Cognitive domains which are mainly involved in DLB are short term memory, attention, executive function, and visual-spatial orientation [4]. The same cognitive functions may be also impaired in PDD, but attention, executive functions, and episodic memory are usually worse in DLB than in PDD [30, 31].

The impairment of short-term memory in DLB reflects problem of retrieval of stored information (which can be improved with cues) rather than encoding new information. In AD in turn, patients may have a problem of encoding new information. Interestingly, also the rate of cognitive decline is higher in DLB than in PDD [32, 33, 34].

Additionally, diagnostic criteria for PDD [12, 35] require not only cognitive impairment in many cognitive domains, but also mood disturbances, most frequently depression, in addition to visual-spatial deficits similar to DLB.

PET and post-mortem studies reveal more advanced cortical atrophy, more depositions of alpha-synuclein in cortical and limbic regions, as well as amyloid and tau protein burden, typical for AD, in DLB than in PDD. These changes may explain earlier onset and greater intensity of cognitive deficits in DLB. It is worth noting that PET studies have not revealed differences in cholinergic or dopaminergic deficits between these two disorders [22].

### Neuropsychiatric manifestation

Typically, patients with DLB have recurrent complex,

visual hallucinations. These hallucinations are well formed, and typically include adults, children or animals [4]. At the beginning of the disease, these hallucinations are usually unimodal, without sound, smell, or touch. Later, they become more complex. They are generally well tolerated by the patients, and they are emotionally neutral. Occasionally, they may become dysphoric or cause fear in the patients.

Visual hallucinations are present in about 54–70% of DLB subjects and are less frequent in PDD (45–60%) [22]. Hallucinations in DLB usually occur spontaneously, and they are probably related to the presence of Lewy bodies in the temporal lobes [36]. In PDD visual hallucinations usually are secondary to dopaminergic therapy [10, 11], although may also occur in drug-naïve PD patients or patients taking very low doses of dopaminergic drugs [37].

DLB patients may have their visual hallucinations aggravated by dopaminergic therapy, but the same applies to PDD [22].

Delusions can also be observed in DLB, usually of paranoid type. Delusions of infidelity are very common in DLB, also delusions of unknown people in the house. Later in the course of the disease, so called Capgras syndrome may occur. Capgras syndrome is a disorder, when someone believes that a person close to him/her has been replaced by a duplicate. The reason for the Capgras syndrome is probably inability to retrieve emotional associations.

### Fluctuations of attention and cognition

Both DLB and PDD patients may have fluctuations of attention and arousal. The variability of attention occurs in both disorders, more often in DLB – 42%, whereas in PDD this frequency is about 29% [12].

Damage within the thalamus and cholinergic imbalance may probably be responsible for cognitive fluctuations [38]. Fluctuating cognition is manifested by: inconsistency in behavior, speech, variability in attention and awareness. A specific feature of the fluctuations in the course of DLB is their presence at the onset of the disease, which distinguishes them from fluctuations in the advanced stages of other dementias [1].

### Parkinsonian syndrome

Parkinsonian syndrome is usually symmetrical, with predominance of bradykinesia and gait problems [4]. Parkinsonian symptoms in the course of DLB has a prevalence between 60 and 92% [39, 1]. Interestingly, about 25% of DLB patients never develop parkinsonian symptoms throughout the course of the disease [40, 41].

There is a large variability among patients in terms of the severity of motor symptoms [4]. In DLB bradykinesia and rigidity are generally more common [42], while rest tremor is less common [43]. Definitely, there is a difference

between DLB and PDD patients in levodopa response. Contrary to PD subjects, DLB patients usually have poor and limited response to levodopa or other dopaminergic drugs.

DLB patients will develop parkinsonism of increasing severity over a few years with a prevalence between 60 and 92% (40), although 25% of DLB patients never develop parkinsonian symptoms (40, 41).

### Hypersensitivity to neuroleptics

This hypersensitivity is caused by loss of dopaminergic cells [4]. Additionally, dopamine blocking agents may exacerbate parkinsonian syndrome, which is not beneficial effect both in DLB and in PDD. The occurrence of neuroleptic hypersensitivity does not differ significantly between PDD and DLB [44].

Sometimes this aggravation of parkinsonian syndrome can be even irreversible. Interestingly, DLB patients are also at higher risk for neuroleptic malignant syndrome. Neuroleptics given in these two groups of patients may also affect cognition and deteriorate attention and alertness. DLB and PDD subjects are especially sensitive to D2 receptors blocking agents, and these agents are contraindicated in both these disorders.

### Other less frequent symptoms

Some symptoms, like RBD (REM sleep behavior disorders), hyposmia and constipation are also common for these 2 disorders and may even precede the onset of other symptoms by several years [45]. Interestingly, these abnormalities are risk factors also for other synucleinopathies, like MSA. REM sleep behavior disorder is lack of normal muscle atonia during the REM sleep. As a consequence, people act out their dreams.

REM sleep is the phase of sleep in which vivid dreaming is present. Lack of normal motor atonia in this phase may lead to different behavioral abnormalities during sleep, like punching, kicking or yelling. It is worth noting that the presence of RBD is not specific to DLB only, as it can be present in other synucleinopathies, including PD.

Autonomic dysfunction in PDD and DLB is not as evident as in MSA, but symptoms of autonomic failure may also occur in Lewy body dementias. The most frequent are constipations, present in both of these disorders.

Other reported by the patients autonomic problems are orthostatic hypotension, syncope and falls, which usually occur in later stages of DLB and PDD. Neurogenic urinary frequency or incontinence may also occur in both of these disorders.

### The treatment

Due to the loss of cholinergic and dopaminergic

neurons in PDD and DLB, the use of cholinesterase inhibitors and dopaminergic drugs is justified. Until now, no disease modifying drugs have been registered for the treatment of these disorders. Placebo-controlled clinical trials confirmed efficacy of donepezil and rivastigmine in the treatment of cognitive decline in DLB and PDD [46].

In some patients cholinesterase inhibitors may be also effective in reduction of psychiatric manifestation, like hallucinations and delusion.

Carbidopa/levodopa in doses 25 mg/100 mg respectively, given 2 or 3 times a day can reduce parkinsonian features, usually without negative influence on cognition or psychosis. Of course this positive effect on the reduction of parkinsonian signs is more beneficial for PDD patients.

### Conclusions

DLB and PDD are similar disorders in terms of clinical manifestation and neuropathological abnormalities, they also share common genetic, pathophysiological and neuroimaging features.

The most important clinical features of both these disorders are dementia, parkinsonism, hallucinations, and fluctuations of attention and arousal. Additionally, both of them belong neuropathologically to synucleinopathies. Additionally, patients with Lewy body dementias may have superimposed neuropathological changes typical for AD, which are also frequent.

Due to marked loss of cholinergic and dopaminergic neurons both in DLB and PDD, there is significant impairment in cholinergic and dopaminergic transmission, which requires treatment with acetylcholinesterase inhibitors and levodopa. Disease modifying treatment has not been introduced for none of these disorders, and is still an important but unmet need.

The distinction between these two disorders is mainly based on the relative timing of the onset of cognitive and parkinsonian syndrome (the rule of 1 year). That is why the hypothesis occurs, that maybe they should be treated as one disorder within the clinical spectrum of Lewy body disease.

### Conflict of interest

The author has declared no conflict of interest.

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