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DEMENTIA WITH LEWY BODIES AND PARKINSON'S DISEASE DEMENTIA

Vladimira Vuletić[a,b] *and Nenad Bogdanović*[c,d]

[a]Clinical Department of Neurology, University Hospital Centre Rijeka, Rijeka, Croatia

[b]Medical Faculty University of Rijeka, Rijeka, Croatia

[c]The Aging Brain, Theme Aging, Karolinska University Hospital R94

[d]Karolinska Institutet, NVS, Stockholm

Summary

Dementia is a frequent but often unrecognized problem in advanced stages of Parkinson's disease (PD). The point prevalence of dementia in PD patients is around 30% and around 10% of a PD population will develop dementia per year. Risk factors and different biomarkers have been studied trying to predict pre-dementia stages of cognitive impairment in PD and finding neuroprotective treatments. Dementia with Lewy bodies (DLB) is also an often-unrecognized neurodegenerative disease. It is the second most common neurodegenerative dementia after Alzheimer's disease. Incidence of Lewy body dementias is 5.9 cases per 100,000 person-years. It shares some clinical, genetic, neurochemical, morphological and pathological features with Parkinson's disease (PD), Parkinson's disease dementia (PDD) and has unknown etiology. Nevertheless, they differ in timing of cognitive, behavioral and motor symptoms, medications response, and neuropathological contributions. Despite new diagnostic criteria, both dementias are often misdiagnosed and untreated. In this article, we review the current knowledge regarding cognitive impairment and understanding of dementia and overlapping symptoms in PDD and DLB

Key words: Dementia with Lewy bodies, Parkinson's disease dementia, overlapping and controversies

Parkinson's disease dementia (PDD)

Dementia is a frequent but often unrecognized problem in advanced stages of Parkinson's disease (PD). Usually, PD is considered as mostly a motor disease with known cardinal symptoms (*tremor*, *bradykinesia/akinesia*, and *rigidity*), but non-motor symptoms are influencing the quality of life and earlier institutionalization of PD patients [1]. The point prevalence of dementia in PD patients is around 30% and around 10% of a PD population will develop dementia per year what is four to six times greater than in subjects without PD [2]. In a general dementia population, 3 to 4% of cases are due to Parkinson's disease dementia **(**PDD) [3]. It is known that the longitudinal development of dementia is: progressive rates of 26% at 3 years, 28% at 5 years, and 48% at 15 years [4] and an 8-year cumulative prevalence of PDD in elderly PD patients is of 78% [5]. Although cognitive impairment can exist at time of diagnosis, the mean duration of PD before dementia develops is approximately 10 years [5,6].

Risk factors for PDD studied so far are: higher age, more severe parkinsonism, in particular rigidity, postural instability and gait disturbance, and mild cognitive impairment at baseline; and also, male gender, education, depression, visual hallucinations can influence on that [7]. Cognitive impairment in PD can vary from subjective cognitive decline, mild cognitive impairment to PDD and includes attentional, executive, visuospatial, and memory dysfunctions. Cognitive problems and dementia are more common in PD patients with akinetic/rigidity type [5]. A task force of the Movement Disorder Society developed diagnostic criteria for PD dementia that includes demonstrable slow progressive impairment in more than one above-mentioned cognitive domain and with at least one behavioral symptom (apathy, depression/anxious mood, hallucinations, delusions or excessive daytime sleepiness) [8].

Most neuropathological studies indicate that the presence of cortical and limbic Lewy bodies and Alzheimer's disease (AD) pathology (neurofibrillary and amyloid-β plaque) correlates with the severity of cognitive impairment [9,10]. The Braak hypothesis of a caudal to rostral progression of the disease, including the involvement of the cortex is well-known [11]. Several neurotransmitters including dopamine, acetylcholine, noradrenaline, and serotonin may contribute to PD cognitive impairment in accordance to marked loss of limbic and cortically projecting dopamine, noradrenaline, acetylcholine and serotonin neurons. [10].

There are many different biomarker studies and efforts (from laboratory to novel structural and functional imaging techniques) trying to find biomarkers of pre-dementia stages of cognitive impairment in PD, when we can try with re-

searching of some neuroprotective treatments. However, no biomarker has yet been validated. Nevertheless, low levels of epidermal and insulin-like growth factors or uric acid in plasma/serum and of Aß in CSF, reduction of cerebral cholinergic innervation and glucose metabolism measured by FDG- PET mainly in posterior areas, and hippocampal atrophy in MRI might be indicative for risk of dementia in PD patients [12].

There are known role of the APOE*ε4 allele, Glucocerebrosidase (GBA) mutations and mutation in gene encoding for α-syn (SCNA) and triplications in cognitive decline in PD, whereas the findings are mixed for Microtubule-associated protein tau (MAPT) polymorphisms [13]. Dementia can be seen in familial forms of PD in the Parkin gene mutations, PARK1 and PARK8 and is rare in PARK2, PARK6, and PARK7 [14]. In every-day practice, we are using published criteria and tests to identify cognitive deficits in PD [15]. An increase in low frequency (delta and theta) EEG spectral power distinguishes PDD from PD and AD [16].

There is still a lack of effective treatment of PDD. Only rivastigmine has got the approvement of Food and Drug Administration. Other cognitive enhancing medications have some mild effect in PD dementia. A cognitive training, physical excersize and neurostimulation have some promising results [17-20].

Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative dementia after Alzheimer's disease and the most common neurocognitive disorder with Lewy bodies, but often passed unrecognized. Nevertheless, DLB is often missed and misdiagnosed with AD and PDD so appropriate treatment is late and distressing side effects, due to inappropriate drug prescription, can be caused.

It accounts for 25% of all dementias [21]. Incidence of Lewy body dementias is 5.9 cases per 100,000 person-years and prevalence very from 3 to 26.3% over the age of 65 years. In addition, in a population-based study, 7. 6% of dementia cases were diagnosed as dementia with Lewy bodies. Life expectancy after disease onset is 5-7 years [21]. Risk factors of (DLB) include advanced age, hypertension, hyperlipidemia, and carriers of one or more APOE ε4 alleles. However, presence of APOE ε4 may be an important predictor of more rapid decline [22]. Neuropathological characteristics are deposition of α-synuclein in Lewy bodies, Lewy neurites and Lewy dots, loss of tegmental dopamine neurons and basal forebrain cholinergic neurons but also in 25-50% of cases full blown Alzheimer pathology (β-amyloid deposits and tau neurofibrillary tangles) is present. There

are also deficits of GABA and serotonin neurotransmission [22]. The new consensus of DLB diagnosis points clinical signs and symptoms as core or supportive and biomarkers as indicative or supportive [23].

Progressive cognitive problems in DLB have features of cortical and subcortical dementia that interferes with normal social or occupational functions, or with usual daily activities. Mostly the initial clinical features of DLB include confusion, memory disorders, and impaired judgment. Patients with DLB have more prominent impairment of attention, executive functioning, visuospatial problems, more difficulties in clock drawing or figure copying as compared to patients with Alzheimer's disease who have more prominent memory changes on Mini Mental State Examination [24]. **The essential feature** for diagnose of DLB is dementia. **Other core** characteristics are early hallucinations (mostly visual and well formed), fluctuating attention and alertness (delirium-like), extrapyramidal signs (Parkinsonism- one or more cardinal features like bradykinesia, rigidity or resting tremor) and Rapid Eye Movement (REM) sleep behavior disorder (RBD) which usually precede cognitive problems and is present in 76% DLB patients [23]. Sometimes, parkinsonism is an initial symptom and then the 1-year rule is very important to distinct DLB from PDD. However, parkinsonism is very common core symptom in over 85% DLB patients [23]. Documentation of only one of the cardinal features, bradykinesia, resting tremor, or rigidity, is required for DLB, while at least two are required to diagnose PD.

Supportive clinical features in the new criteria are: severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression. In new criteria, a severe antipsychotic sensitivity is named as supportive, because reduced prescribing of D2 receptor blocking antipsychotics in DLB limits its diagnostic usefulness [25].

The indicative biomarkers are: a) visualization of reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging using a ligand that binds to presynaptic dopamine transporters N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) DAT-Scan. b) abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy and c) polysomnographic confirmation of REM sleep without atonia.

The supportive biomarkers in new criteria are: a) relative preservation of medial temporal lobe structures on CT/MRI scan, b) generalized low uptake on SPECT or FDG-PET perfusion and metabolism scan, respectively, with reduced occipital activity called the cingulate island sign on FDG-PET imaging

and c) prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/ theta range are named as supportive biomarkers [26].

In addition, importance of EEG specific abnormalities in posterior derivations is pointed in new criteria due to a predictive value of 90% for the diagnosis of DLB compared with AD and correlate positively with the severity of clinically observed cognitive fluctuations [27].

Amyloid PET imaging shows increased amyloid β brain deposition in 50% of patients with DLB, but presence of tau and medial temporal lobe atrophy are key indicators of coexisting AD pathology in DLB, known predictor of clinical phenotype and progression [28,29]. Two assessment toolkits are built to improve the diagnosis of DLB [30]. In management of LBD patients, knowing disease's specificities and multidisciplinary approach are very important. Due to frequent sensitivity to some medications, it is recommended to start cautiously at low dose tracking the most troublesome problems. There are no medications approved especially for DLB and no disease-modifying agents. A treatment is still symptomatic and include pharmacological and nonpharmacological treatment mostly for cognitive, neuropsychiatric, motor and sleep disturbances. Rivastigmin more than donepezil is preferred for cognition, quetiapine, risperidon and clozapine for visual hallucinations. For depression mirtazapine is more preferred than selective serotonin or serotonin-norepinephrine reuptake inhibitors, due to the side effects of later ones. For parkinsonism, levodopa in lower doses is better than dopamine agonists, and clozapine and melatonin for RBD. Memantine is suggested to be add on dopamine medication. Orthostatic hypotension can be treated with non-pharmacological approach: hydration, salt tablets, compression stockings, avoidance of exacerbating medications, and in hard cases pharmacologicaly with fludrocortisone and midodrine. It is very important that dosing and medication selection are individualized considering degree of functional impact of symptoms being targeted and side effect thresholds. Occupational therapy, physical therapy, speech therapy such as Lee Silverman Voice Therapy, cognitive training, exercise, active social life and other lifestyle changes are very important in all neurodegenerative diseases [31].

DLB/PD/PDD: CURRENT CONCEPTS OF OVERLAPPING AND CONTROVERSIES

Parkinson's disease (PD), Parkinson's disease dementia (PDD), Dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and peripheral autonomic failure (PAF) share pathological markers of abnormal α-synuclein aggregation and that group of diseases is called synucleinopathies.

However, DLB and PDD are considered as major neurocognitive disorders with Lewy body pathology, although there are some scientists discussing that they are the same disease [32] the clinical picture differe these two clinical entities. So far, we know that both entities share clinical, genetic, neurochemical, morphological and pathological features, but a comprehensive distinction between them is still missing.

We only have an arbitrary distinction considering the time of onset of motor and cognitive symptoms: dementia often preceding parkinsonism in DLB and onset of cognitive impairment after onset of motor symptoms in PDD (1-year rule) [33]. Dementia occurring in a patient with a pre-existing clinical diagnosis of PD should be referred to as PDD. A cognitive impairment is an early sign in DLB while extrapyramidal motor features are often mild or absent, at least until the late stages. An early and prominent extrapyramidal motor features required for PD diagnosis is a typical characteristic of PDD, with neuropsychiatric and cognitive symptoms occurring later. It is widely accepted that the difference between these two distinct clinical syndromes of DLB and PD/PDD shareing underlying pathomechanisms, could be a different propagation patterns of α-syn pathology across different neuronal pathways. A concomitant AD pathology is more common in DLB as compared to PD/PDD.

It is suggested that they are subtypes of an α-synuclein-associated disease spectrum (Lewy body diseases), which include incidental Lewy body disease, non-demented Parkinson's disease, PDD, DLB, and DLB with Alzheimer's disease [34]. Previous studies have shown more pronounced cortical atrophy, elevated cortical and limbic Lewy pathologies (with APOE ε4), apart from higher prevalence of Alzheimer pathology in DLB than PDD [33]. It can be the cause of an earlier onset, greater severity of cognitive defects, more often attentional fluctuations in DLB. The main clinical overlaps are: rigidity, akinesia, cognitive impairments, frontal executive dysfunction, visual-constructive impairment, mild language impairment, hallucinations (visual), delusions (less frequent), mood disturbances (depression, anxiety), RBD and neuroleptic sensitivity. Known dissimilarities in clinical pictures are: some cognitive dysfunctions: deficiencies of attention greater, episodic verbal memory tasks lower in DLB, tremor significantly less frequent in DLB, motor performance: slower walk and poorer balance in DLB, hallucinations more frequent in DLB, relative timing of dementia and parkinsonism (1 year rule), onset of dementia later in PDD, orthostatic hypotension more frequent in DLB, frontal/temporal-associated cognitive subsets more severe in DLB, cognitive decline is faster in DLB/DLB + AD than in PDD, delusions, attentional fluctuation and visual hallucinations more frequent in DLB,

visual hallucinations: spontaneous in DLB; after L-dopa therapy in PDD, but also in drug-naive patient. Known laboratory overlaps are: decreased DAT-Scan binding in putamen, reduced cardiac MIBG binding, medial temporal lobe relatively preserved (CT, MRI), occipital hypoperfusion in FDG-PET, similar EEG abnormalities, similar metabolic decrease in cerebral cortex, larger width of 3rd ventricle and frontal horns and GBA mutations. Known laboratory dissimilarities discussed lately are: Grey matter cortical atrophy more frequent and more severe in DLB, White matter hypointensities in temporal lobe more severe and more frequent in DLB, Different functional connectivity corticostriatal disruption: PDD: frontal cortical disruption; DLB: parietal and occipital disruption, More severe Aβ brain deposition (PiB uptake) in DLB, Tau-PET imaging more severe in DLB, Several genetic differences (APOE ε4, mitochondrial transcription factor A (TFAM)), Low DAT uptake in caudate related to functional impairment in DLB, not in PDD, SN sonography (size, asymmetry), CSF AD profile more common in DLB and CSF αSyn oligomers increased in PDD. Morphological overlaps are: mixture of cortical and subcortical LB/αSyn and AD-related pathologies, similar Braak LB stages (4–6) and Braak neuritic stages (5 or 6), relation between pαSyn and tau aggregation to Aβ deposition in cortex, initial αSyn aggregation in pre-synapses inducing neurodegeneration via interference with axonal transport, postsynaptic protein downregulation. Known morphological dissimilarities are: higher Aβ load in cortex and striatum in DLB, Aβ phases and neuritic plaque scores higher in DLB, higher cortical LB load in temporal & parietal cortex in DLB, increased tau loads in cortex and striatum in DLB, more frequent and severe αSyn load in hippocampal subareas CA2 in DLB, minor deviations in severity and lesion pattern in SNc, pedunculopontine cholinergic cell loss in hallucinating PDD, but not in DLB, higher 5-HT1A receptor binding in cerebral cortex in DLB [33].

Conclusion

In conclusion, although these disorders overlap in many aspects of their presentations and pathophysiology they differ in other elements such as timing of cognitive behavioral and motor symptoms, medications response, and neuropathological contributions. It is very important to recognize DLB early and to provide the best possible treatment and adequate information to patients and their relatives. In this article, we review the status of knowledge regarding cognitive impairment and current understanding of dementia and overlapping symptoms in PDD and DLB. This should help clinicians to diagnose DLB and PDD at an earlier stage and provide better patient care. Further studies in synu-

cleinopathies are needed for elucidation which patients and when will develop cognitive problems or extrapyramidal symptoms and what are the biological factors that could determine that. That is a prerqusite, towards the sussesful development and implementation of personalized medicine and disease-modifying therapy.

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Corresponding author:
Vladimira Vuletić
E-mail: vladimira.vuletic@gmail.com