Dementia with Lewy bodies and Parkinson’s disease dementia: part of one continuum or two distinct entities?

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Abstract

Point of view: Continuum

Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) are the second most common type of degenerative dementia after Alzheimer’s disease (AD) in patients older than 65 years. For years, there has been an ongoing debate whether DLB and PDD should be considered as part of one spectrum of dementia related to cortical Lewy body disease or whether they are two distinct conditions. One’s position on this debate is normally reflected by viewpoint on the disease itself whether it’s clinical, pathological or genetic. The current consensus criteria recognize the clinical distinction between DLB and PDD using the timing of the onset of cognitive symptoms in relation to motor symptoms (i.e. diagnosis of DLB is assigned when dementia and motor symptoms appear together within 1 year, PDD when dementia occurs >1 year after motor impairment). This “one-year” rule regarding temporal relationship between dementia and parkinsonism is however considered artificial and cognitive impairment is recognized to occur not only in more advanced PD, but also in early, untreated PD patients, and even in those patients with pre-motor syndromes such as REM sleep behaviour disorder (RBD) and hyposmia. There are no clinical symptoms that categorically distinguish DLB and PDD as both may show visual hallucinations, autonomic symptoms, RBD, cognitive fluctuations, and neuroleptic sensitivity. Regarding motor symptoms, DLB patients have been described with more symmetrical parkinsonism, relatively higher rigidity and lower resting tremor but this generally would not lead to high sensitivity in diagnosis. In addition to the clinical similarity, DLB and PDD also share a common neuropathological feature of cortical alpha-synuclein-positive Lewy bodies (LBs) and neurites that does not differentiate DLB from PDD or in fact even from Parkinson’s disease (PD) without dementia. This is reflected in the overlapping staging criteria of the two syndromes that both examine the topographical distribution of alpha-synuclein pathology (i.e. Braak PD stages 1-3= McKeith’s brainstem DLB, Braak stages 4-5= McKeith’s limbic DLB, Braak stages 5-6= McKeith’s neocortical DLB). Generally, most DLB, PDD and PD patients die with end-stage disease at which point the brain is diffusely involved. Some studies have suggested that there is more beta-amyloid accumulation in DLB causing a more aggressive course of disease (i.e. shorter time to dementia) but concomitant Alzheimer-type pathology is also very common in PDD and thus cannot be used as a diagnostic marker to distinguish the two syndromes. The only difference appears to be the nigral neuronal loss which can be more significant.
in PDD than in DLB suggesting that the most vulnerable neurons may differ between these disorders; however this has not been systematically studied. Genetic factors may also play a role in the expression of cognitive deficits in DLB and PDD, as suggested by dominant familial forms of DLB/PDD. Notably, missense mutations in the alpha-synuclein gene (SNCA) and locus multiplications are associated with clinical and pathological phenotypes ranging from PD to PDD to DLB. In worldwide populations SNCA genetic variability remains the most reproducible risk factor for idiopathic PD and SNCA gene has recently been also associated to DLB. However, only few investigators have looked at SNCA variability in terms of the different clinico-pathological groups. We used targeted next-generation sequencing to comprehensively characterize the 135kb SNCA locus in a large multi-national cohort of patients with PD, PDD, DLB and healthy controls. An analysis of 44 tagging single nucleotide polymorphisms (SNPs, with MAF>5%) across the entire SNCA locus showed two distinct association profiles for parkinsonism and dementia, respectively towards the 3’ or the 5’ of the SNCA gene. In addition, we defined a specific haplotype in intron 4 that is directly associated with PDD. The PDD risk haplotype has been interrogated at single nucleotide resolution and is uniquely tagged by an expanded TTTCn repeat. Our genetic study suggests that there may be specific haplotypes that have functional consequences in both mRNA and protein level that explain where in the continuum patients would fall. The fundamental question is the mechanism(s) whereby these subtle allelic differences lead to mismetabolism of alpha-synuclein responsible for the neurodegeneration and subsequent clinical presentation. In order to unravel this, it is important that clinicians, pathologists and geneticists work together each describing the variables they can measure reliably in optimal detail rather than obscuring subtle differences by trying to fit subjects into certain disease categories. Thus, the question whether DLB and PDD are on a continuum or distinct entities is rather moot. Single Lewy body disorder model however is more useful for studying disease pathogenesis with an ultimate aim of developing disease-modifying therapies that target the alpha-synuclein-related neurodegeneration.