Commentary
DLB and PDD: the same or different? Is there a debate?

Debating is a formal method of interactive and position-representational argument. It is a broader form of argument than logical argument, since it can include elements of persuasion in order to appeal to the emotional responses of an audience. For experienced debaters, any proposition can be defended or destroyed and the outcome depends at least as much on his or her persuasive powers as it does on the facts of the matter.

The concept of DLB as a clinico-pathological syndrome "separate" from AD emerged from a series of debates held in Newcastle upon Tyne in 1995 during the first DLB Consortium meeting (McKeith *et al.*, 1996). The point at issue was whether a subset of dementia patients had a "variant" of AD or a different condition. Evidence and persuasion were combined to achieve consensus that many of these patients were sufficiently different from AD clinically and pathologically to warrant them being placed in a separate category for which the term DLB was coined. In doing so the Consortium satisfied the original meaning of the Latin word "debatum," which means to reach an agreement.

The debate in which we are invited to engage by Drs Revuelta, Aarsland and colleagues – namely, the sameness or differentness of DLB and PDD – arose as an unforeseen secondary consequence of these events. By acknowledging a diagnostic category of DLB, the Consortium members generated *en passant* the need for a definition of PDD, since it appeared to them that DLB and PDD could not be said to be the same, a conclusion that was based upon one observation and one opinion. The observation was that up to 25% of autopsy-confirmed dementia cases with LB pathology were not significantly parkinsonian during life, suggesting that they could not realistically be said to have PDD. And the opinion was that DLB and PDD seemed to be quite different clinical syndromes, at least in the early stages, with the burden of impairments falling on different parts of the nervous system in a different temporal sequence. The need for this DLB/PDD divide was stated in the form of the infamous one-year rule which stated that if extrapyramidal motor features had been present for 12 months or more before the onset of dementia, the diagnosis should be PDD but if dementia occurred within 12 months of the motor features, or indeed preceded the motor features, the diagnosis should be DLB. It was acknowledged at the time that this boundary in time was entirely arbitrary and existed solely to draw a line between two overlapping clinical syndromes. A return to this boundary issue at the Third Meeting of the International Dementia with Lewy Bodies Consortium resulted in the following restatement of this basic position:

> The distinction between dementia with Lewy bodies and Parkinson's disease dementia as two distinct clinical phenotypes, based solely on the temporal sequence of appearance of symptoms has been criticized by those who regard the different clinical presentations as simply representing different points on a common spectrum of Lewy body disease, itself underpinned by abnormalities in alpha-synuclein metabolism. This unitary approach to classification may be preferable for molecular and genetic studies and for developing therapeutics. Descriptive labels that include consideration of the temporal course are preferred for clinical, operational definitions. Dementia with Lewy bodies should be diagnosed when dementia occurs before or concurrently with parkinsonism, while Parkinson's disease with dementia should be used to describe dementia that occurs in the context of well-established Parkinson's disease. The appropriate term will depend on the clinical situation and generic terms such as Lewy body disease are often helpful. In research studies in which distinction is made between dementia with Lewy bodies and Parkinson's disease with dementia, the one-year rule between the onset of dementia and Parkinsonism should be used. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings including pathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as Lewy body disease or alpha–synucleinopathy. (McKeith *et al.*, 2005)

Is it possible to resolve the DLB/PDD conundrum by further debate? Not even the most articulate, persuasive and well-informed protagonist could persuade me that the clinical presentation of a patient with a ten-year history of PD proceeding to dementia is the same as that of the patient with probable DLB who presents with fluctuating confusion and hallucinations. But these probably represent the extremes of the spectrum and the debate should be focused on how one might classify the patient who presents with (say) the insidious onset of mild Parkinsonism and forgetfulness, or with visual hallucinations early

in the course of PD. Neither PDD nor DLB seems particularly appropriate for either of these rather different clinical situations, although both patients are probably destined to reach a similar end stage of dementia and Parkinsonism if they live long enough. Which suggests (although does not prove) that both patients have the same "thing" wrong with them, i.e. disease state, and are simply manifesting it differently in the early stages. So what should we call this disease state? It would be unhelpful to generate more clinical diagnostic labels to cover all the possible combinations and variations in presentation that can and do occur associated with Lewy body disease, especially if we include dysautonomia and sleep disorders which dominate the picture in some patients. If we did so, we would end up with a dozen or more different clinical epithets.

Which is why the Third DLB statement is worded as it is. DLB and PDD describe two clinical presentations that are sufficiently different clinically to warrant different labels and which, as Revuelta and Lippa suggest, are probably better dealt with by a cognitive disorder or movement disorder specialist respectively. For patients who don't fall into one of these categories, use of the term Lewy body disease, accompanied by a description of the presenting symptoms, may be much more appropriate. e.g. "Mrs. H has a four-year history of Lewy body disease, presenting first with postural-instability, gait-difficulty Parkinsonism and with the later development of orthostatic hypotension, visual hallucinations and moderate dementia."

The more subtle point, to which Aarsland *et al.* apply most of their persuasive energy, is the extent to which we can be sure that these different clinical syndromes are truly representations of the same underlying disease. Revuelta and Lippa cannot really produce any convincing evidence that there are any major pathological, neurochemical or imaging parameters that vary substantially between DLB and PDD, and their analogy of cerebrovascular disease being a common process, responsible for a multitude of different clinical presentations, implies that they conclude much the same about Lewy body disease, effectively, agreeing with Aarsland *et al.* They go on to elaborate that "cortical LBs and LNs are the principal pathologic entity responsible for the clinical dementia syndrome in both PDD and DLB and correlate well with severity of dementia in both entities." Although in a gross anatomical way this argument may stand up, with brainstem LB disease approximating to motor PD and cortical LB disease being associated with dementia, the story is clearly more complicated than this. The current model which views LB and LN as the key pathogenic lesions of LB disease has been challenged by a recent report that the majority of aggregated α-synuclein is located neither as LB nor as LN but as much smaller molecular weight moieties located in presynaptic terminals (Kramer and Schulz-Schaeffer 2007). These authors further suggest that these aggregates may be synapto-toxic, causing an almost complete loss of dendritic spines in the post-synaptic area. One can see an analogy with recent debate about which species of amyloid are toxic in AD, low molecular weight oligomers being implicated in inhibiting long-term potentiation, enhancing long-term depression and reducing dendritic spine density in the normal rodent hippocampus, through activation of metabiotropic glutamate receptors and N-methyl D-aspartate receptors (Selkoe, 2008). Until we have a more complete understanding of the corresponding patho-biology of α -synuclein related neurodegenerative disorders, it may be premature to engage in weighty debate as to whether DLB and PD are the same or different in such regard.

The revised DLB diagnostic criteria also propose that the additional presence of Alzheimer type pathology colors the clinical presentation very considerably. Two recently published papers support this notion. Weisman *et al.* (2007) found only one third of a series of 95 autopsy-confirmed LB pathology dementia cases to have the probable DLB syndrome, these cases generally having only limited Alzheimer pathology. By contrast, Fujishiro *et al.* (2008) found 90% of diffuse cortical LB cases with Braak neurofibrillary tangles up to stage 5, to have probable DLB clinically, compared with only 20% with Braak Stage 6. Taken together, the evidence suggests that what we as clinicians call DLB is itself a rather heterogeneous and variable "entity" and we would do well to bear that in mind.

So does any of this debate matter? Are PDD and DLB not simply two contrived syndromes that have some limited clinical usefulness but which are of little other consequence? The answer to this depends upon what we see as the value of what we can do for our patients and their families. Clinicians have a duty to make diagnoses that describe and explain as fully as possible what the patient is reporting and to use that diagnosis to make management decisions and offer a prognosis. It matters profoundly that we understand the nature of the diagnostic categories that we are using, and that we appreciate how they relate to underlying biological processes. DLB and PDD are the handles by which we can hold and manipulate this complex disease area and without them we would struggle, even more than we do already, to communicate either with our patients or with each other. But even as we use the terms we have to be prepared to admit to gaps in our understanding, and to tolerate the fact

that the system is less than perfect. I am encouraged that despite Revuelta and Lippa and Aarsland and colleagues having been set up to debate a difference, they in fact appear to be arguing in the same general direction. I agree with them both.

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