International Psychogeriatrics (2004), 16:2, 123–127 © 2004 International Psychogeriatric Association
DOI: 10.1017/S1041610204000328 Printed in the United Kingdom

GUEST EDITORIAL

Dementia with Lewy bodies and other difficult diagnoses

The last two decades have seen psychogeriatrics transforming into a fast-moving, science-led specialty. This is particularly so in the field of dementia, spurred on as it so often is, by the findings of high-tech neuroimaging and molecular pathology. Clinicians are required in their daily practice not just to make the traditional diagnostic distinctions between dementia, delirium, pseudodementia and "normal aging," but are expected in this new world also to recognize a series of different dementia subtypes, including Alzheimer's disease (AD), cognitive vascular impairment (CVI), dementia with Lewy bodies (DLB), fronto-temporal dementia (FTD) and prion disease. The list could go on and on (and sometimes does). We also know from autopsy studies that mixed pathology dementia cases are common and that our clinical diagnoses should take this into account.

But can the splitting of dementia into a multiplicity of overlapping clinical syndromes really be justified? The most compelling argument is that each "disorder" has different symptoms, clinical course and responses to treatment. This is possibly true of pure forms, but is a harder position to sustain for the many mixed cases that we see every day. A second proposition offered is that different dementia subtypes are "caused" by dysregulation of specific neuronal proteins. Thus disorders like AD, characterized as tauopathies, will require different preventative pharmacological approaches compared to synucleinopathies such as DLB.

The splitters have generally reinforced their approach by the elaboration of sets of operationalized clinical criteria for their different clinicopathological entities. NINCDS-ADRDA, NINDS-AIREN, Consensus DLB and Manchester-Lund criteria for FTD are all widely known and used. Their particular value has been to standardize diagnostic practice internationally, promoting interrater reliability and increasing the likelihood that a case diagnosed as AD or DLB in one setting will correspond closely to cases with the same diagnosis elsewhere. This in turn has permitted clinically-based research studies to go ahead. Multicenter drug trials, genetic association studies, epidemiological risk factor estimations and many other activities all rely upon accurate and valid segregation of diagnostic groups.

But these operationalized criteria are very much less than perfect. They generally describe the "pure" rather than the typical case and, as a consequence, err on the side of high specificity at the cost of limited sensitivity. In other words, a relatively small number of dementia cases meet the various stringent criteria

for "probable" AD, DLB etc., although if they do, they are likely to be correctly classified. The creation of a "possible" diagnostic category apparently deals with a lot of the atypical cases, although autopsy follow-up studies show that these "possible" diagnoses are seldom better than 50% accurate. It appears that we have developed a diagnostic system that caters very well for a few cases, but which might be criticized as inadequate for the majority. Anyone who has used one of these operationalized diagnostic schemes, will be familiar with the cry that the majority of patients "failed to meet the criteria." Or being more honest, that the criteria failed to meet the majority of the patients.

Where does resolution of these diagnostic problems lie? Is it simply a matter of improving the criteria? Or is there a more fundamental issue to be addressed? How valid an exercise is it to split dementia into a reliable categorical classification? Nowhere have these arguments been more exhaustively rehearsed as they have around the developing concept of DLB. Twenty years ago there was no such diagnostic label. Review of autopsy series from that period demonstrate that the cases existed, but until the late 1980s, patients with parkinsonism, visual hallucinations and fluctuating cognition were generally labelled as having atypical AD, delirium of unexplained etiology, or both. A decade later, once the characteristic neuropathology was more widely recognized, two main diagnostic terms had come into use, the Lewy body variant of AD and the consensus label of DLB. These terms reflected two fundamentally differing opinions about what might be "causing" symptoms in these patients. Since there were usually abundant beta-amyloid plaques present, identical to those seen in classical AD, this raised the possibility that this remained the primary pathology with LB as a secondary, modifying factor. The other camp argued that LB could themselves be a sufficient cause, although had to concede that they sometimes occurred at very low density in the brains of even severely demented patients. The discovery of a widespread, alpha-synuclein positive, neuritic degeneration resolved this low LB density conundrum. Symptom formation was attributed to disruption of neuronal function by these abnormal Lewy neurites (LN) and the LB became recast as potential good guys, sequestering alpha-synuclein and other toxic protein fragments inside neurons in an attempt to render them less harmful.

Whichever diagnostic term was used however, autopsy studies continued to find that many cases with LB and LN pathology lacked the characteristic clinical features by which patients could be detected during their lifetime. Paradoxically, this was not universally regarded as a bad thing. Failure to recognize a patient who might be susceptible to an adverse neuroleptic sensitivity reaction is clearly undesirable. But for many clinicians working within restrictive guidelines for cholinesterase inhibitor use, it can be much easier to prescribe for a diagnosis of AD than for one of DLB. This illustrates that the value of clinical

diagnoses may be determined as much by their utility as by their scientific accuracy.

In an effort to review and clarify current knowledge, concepts and methods for further enquiry, a specialist meeting was organized by the International Psychogeriatric Association (IPA) in Budapest in November 2002, with the participation of the European Movement Disorder Society (MDS). Participants were asked to systematically review the current state of scientific knowledge about DLB and identify key issues requiring clarification and research necessary to advance knowledge in this area. A brief report of this meeting written by John O'Brien was published very shortly after the event in *IPA Bulletin* and a full review appears in the January 2004 issue of *Lancet Neurology.* This sharing of information focused minds on the important issues needing resolution and provided a timely springboard for the third International Workshop on DLB and Parkinson's disease with dementia (PDD), held over $2\frac{1}{2}$ days in Newcastle-upon-Tyne in September 2003. It is too soon to know how important "DLB3" will prove to be in shaping opinion. Some deliberation and writing is still in progress and the final report, which will update the 1996 and 1999 Consensus papers is expected to appear later this year. But even in anticipation of this, there are some issues that can be commented upon including some which may be extended beyond DLB itself, to dementia diagnosis in general.

Possibly the most important single shift at the Newcastle meeting was that both PDD and DLB were considered together under a common heading. The original DLB Consensus discussions in 1995 were predominantly held between dementia researchers who were primarily interested in delineating DLB from other dementia types. PD was not a pressing clinical issue for most of them, hence their ready acceptance of a "one-year" rule to deal with (dismiss) patients who presented with 12 months or more of extrapyramidal motor features before dementia ensued, and who were therefore classified as having PDD rather than DLB. This was acknowledged at the time as a purely arbitrary threshold, set for convenience at that particular moment. The Newcastle DLB3 meeting heard evidence that this probably was too simple a solution. The nature of the relationship between PDD and DLB is of considerable theoretical and practical significance and requires better clarification.

New research suggests that the majority of PD sufferers will develop dementia, typically occurring 10 years or more after the onset of motor symptoms. In many cases it starts with attentional dysfunction, daytime drowsiness, subtle executive dysfunction and visuo-spatial deficits. It typically progresses to a clinical and pathological end-point indistinguishable from DLB. Other than chronological course, no major differences between DLB and PDD have been found in any variable examined, including cognitive profile, neuropsychiatric features, severity of parkinsonism or responsiveness to cholinesterase inhibitors.

https://doi.org/10.1017/S1041610204000328 Published online by Cambridge University Press

Exactly what causes dementia in PD remains unclear – LB formation, synuclein pathology, additional Alzheimer pathology (usually plaques), neuron loss or neurochemical deficits. The questions being asked about the nature of PDD are therefore the same as those that remain unanswered about DLB. Both "groups" of patients probably belong to a common family of LB disease – the order of onset and severity of individual symptoms varying according to factors as yet undetermined. Age is clearly important. LB disease starting in middle age is highly likely to start as motor PD; in late life it presents as cognitive decline and dementia. Even in rare familial cases attributable to a duplication in the alpha-synuclein gene, this clinical heterogeneity is seen.

Labels such as PD, PDD or DLB may do little more than describe the order of onset of symptoms within a single diagnostic entity, which can best be called Lewy body disease. Perhaps then we should be making this our primary diagnosis, qualified by a secondary descriptive epithet e.g. LB disease with parkinsonism, or LB disease with dementia, or LB disease with parkinsonism and dementia. This suggestion is intellectually more satisfying than the current and rather dislocated system. It also allows more flexibility to change diagnosis as the profile of symptoms alters. A major objection when this was proposed in the Newcastle meeting was that, since LB are only visible on pathological examination, only a clinician with divine powers or of supreme confidence could make a lifetime diagnosis of LB disease. Taken to its extreme, this argument is correct. But we already infer the likely presence of particular pathological lesions that we cannot see until after the patient has died, when we diagnose AD or indeed any other type of dementia. So a clinical diagnosis of "probable" or "possible" LB disease, accompanied by a brief description of the current symptomatic presentation using existing terminology, would not seem unreasonable, and might be acceptable to splitters and lumpers alike.

What about the boundaries of DLB with other dementias? Diagnostic sensitivity for DLB is low not in all cases, but predominantly in those with high Braak AD stages (neocortical tangles) at autopsy. Such patients typically have little in the way of cognitive fluctuation, visual hallucinations or parkinsonism, by which they can be clinically recognized. How might we do this? Visualization of the nigro-striatal dopaminergic system, using the dopamine transporter ligand FP-CIT and SPECT imaging, is one potential biomarker that has already been shown to predict pathological findings at autopsy more accurately than clinical diagnosis can do. The use of biological markers as an adjunct to clinical diagnosis of dementia subtypes is on the horizon and we will need to start adapting our practice to accommodate it. One could envisage measuring vascular, Alzheimer and LB bio-markers in order to quantify the relative amounts of different pathological processes present in any given case. This would refine the process whereby we already recognize many dementia cases as being mixed in type. There

would be a shift away from categorical classification, with all its limitations, and a move to profiling each individual, based upon the underlying pathologies and symptomatic presentation. So a patient might in future be diagnosed with combined LB disease (based on dopamine transporter scan), and Alzheimer pathology (decreased CSF β–amyloid 1–42 and increased CSF phospho-tau), presenting with dementia but no other specific features. This is a more accurate classification than the possible or probable AD diagnosis that such a patient would currently be given. And probably more helpful to the clinician, trying to decide whether to prescribe neuroleptics or cholinesterase inhibitors, when symptoms such as visual hallucinations occur.

Finally, we must remember the needs of patients and families, who look to us for a clear and consistent message about diagnosis, as an essential starting point to dealing with their particular illness. There is already research evidence that we could improve our performance in disclosing diagnoses to people with dementia. We should bear this in mind as we devise our new terminology and be sure that whatever we come up with is not only scientifically valid but will also be useful and usable in the clinic.

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https://doi.org/10.1017/S1041610204000328 Published online by Cambridge University Press