EDITORIAL

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Lewy body dementia: myth or mystery?

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Introduction

Psychiatry is a medical discipline long on disorders and short on explanations.[1] The current debate concerning Lewy Body Dementia is surely enough to confirm this verdict. Although reports only number 300 cases, its rise to prominence has been rapid, provoking heated exchange in the literature and leading more recently to a demand for a review of existing clinical (and histological) classification systems.[2]

Lewy body dementia (LBD) (for the sake of nosological neutrality since up to 20 different rubrics currently exist) has been variously hailed as a new form of dementia with a distinct clinicopathological profile, so called diffuse Lewy body disease (DLBD) or senile dementia of the Lewy body type (SDLT), a variant of Alzheimer's disease – the Lewy body variant of Alzheimer's disease LBV or as part of a spectrum of Lewy body disorders including Parkinson's disease.

What is the clinician to make of this nosological quagmire and has any advance really been made since the early reports of 1961?

It seems clear that LBD is not a new illness and that it represents improved neuropathological detection and a higher index of suspicion which have highlighted its presence. The research base, although small, has identified several important considerations which suggest that LBD should not be ignored.

Firstly, prevalence rates in several studies[3,4] confirm that it is not uncommon.

Secondly, it seems related to two major neurodegenerative conditions, Alzheimer's and Parkinson's diseases.

Thirdly, in the face of mounting clinical and genetic evidence for the heterogeneity of Alzheimer's disease (perhaps accounted for, in part by LBD) and the contamination of existing research data, we require an urgent revision of the current classification system.

Lewy bodies

Lewy bodies (LBs) are eosinophilic intraneuronal inclusion bodies which are the pathological hallmark of a number of neurodegenerative conditions including Parkinson's disease. LBs consist of abnormal accumulations containing the protein ubiquitin and phosphorylated and non-phosphorylated neurofilaments, important components of the neuronal cytoskeleton. Neurofilaments play an important role in axonal transport and determination of axonal calibre. Transgenic animal studies demonstrate that abnormal neurofilament accumulation can lead to neuronal dysfunction and degeneration .

Over the years there has been increased recognition from postmortem studies that LBs also occur in the cerebral cortex in a substantial number of patients with dementia. The numerous rubrics mentioned above have arisen because of the differences between the clinical syndromes which have been described to date in association with cortical Lewy bodies and the diagnostic significance attached to them. Review of the literature suggests differences in the sampling frames from which patients have been drawn may be responsible.[5]

Despite the apparent nosological confusion, a consensus is arising that most research groups are probably referring to a similar condition characterised at the neuropathological level by subcortical and cortical LBs formation, with or without a variable amount of Alzheimer-type pathology, predominantly senile plaques, with only a minority of patients having sufficient neurofibrillary tangles to meet quantitative neuropathological criteria for AD.

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The existence of some cases of LBD in the absence of any accompanying AD pathology and one study[6] linking the number of cortical LBs to severity of dementia strengthen the case for the cortical LBs as a pathological substrate.

Clinical evidence

At the clinical level debate continues on whether there is actually an identifiable syndrome which distinguishes the dementia associated with Lewy bodies. Most clinical evidence against this position comes from studies in which patients diagnosed in life as having AD, according to NINCDS-ADRDA criteria[7,8] were found to have coincident LB pathology at postmortem.

Prospective examination of these subjects was unable to identify characteristic clinical features which might help to distinguish demented patients with LB from demented patients without LB. Protagonists have therefore argued that this proves the case for an AD variant. Others have argued that these cases are really misdiagnosed LBD and represent a small group of Lewy body patients who present with a "typical Alzheimer-type clinical picture". The NINCDS-ADRDA criteria would automatically exclude those with eg. Parkinson's disease or confusional states considered by current operational criteria to be central to the clinical picture.

In this context, it may be important to consider a major influence on clinical and histological classification systems for dementia. The early work of Tomlinson[9] has formed the basis for those currently in use. This emphasised the need to discriminate between AD and vascular dementia, demonstrated in postmortem studies in the 1960s to represent the two commonest causes of dementia in the elderly. Undoubtedly, this bias inherent in the current classification system accounts for some of the evidence which favours a Lewy body variant of AD.

Diagnostic dilemma

Operational criteria for Lewy body dementia[10,11] represent the most rigorous attempts yet to define a clinical syndrome based on retrospective analysis of groups of neuropathologically proven cases of LBD. Systematic attempts to examine the reliability and validity of the criteria show that both have an acceptable reliability and the Newcastle criteria have a satisfactory sensitivity.[12]

If pathologically validated LBD patients are known to be erroneously diagnosed because they meet existing criteria for AD or vascular dementia where does this rather daunting picture leave the ordinary clinician? The operational criteria suggest that a typical LBD presents as a progressive dementia with fluctuating confusion, Parkinsonism and early, marked neuropsychiatric features, particularly visual hallucinations. This suggests an interplay of dual pathology with Parkinsonian features as an important pointer to the diagnosis.

Many features are shared with AD although psychiatric features are more common than in 'pure AD' and extrapyramidal features are milder than in classical PD. Pyramidal symptoms are rare and serve to distinguish LBD from vascular dementia. However, patients who present with cortical symptoms which closely resemble the temporoparietal picture of typical AD present the greatest diagnostic challenge. Surely operational criteria as they undergo a process of refinement and adjustment must seek to identify these patients too?

Genetics

There are hints that molecular medicine may be able to shed some light on the above dilemmas. Taken in total, this evidence supports a clearer link with AD than with PD. For example, a single demented patient has been described from an amyloid precursor protein (APP) 717 mutation family who had both cortical LB and AD pathology, although this was not present in three other families with the same mutation. More compelling, however, is the finding[13,14] that the frequency of the apoE-4 allele, known to be associated with increased risk in familial and sporadic late onset AD, is similarly increased in patients with LBD but not in those with PD.

Cellular and transgenic models to determine the abnormality underlying neurofilament accumulation will help advance understanding at the molecular level still further.

Implications for treatment

Are the nosological disputes mentioned above merely academic or does current diagnostic inaccuracy have practical implications? This is perhaps best highlighted when considering options for pharmacotherapy. LBD patients will frequently have neuropsychiatric presentations and are consequently likely to attract intervention with neuroleptic medication. However, 60% of LBD patients have severe reactions to neuroleptic medication and the risk of mortality is increased two to three fold.[15] Such interventions could prove highly dangerous in the LBD patient. Preliminary evidence suggests that the more selective dopamine antagonists including risperidone and clozapine may be less toxic.

Semi-quantitative analysis of L-Dopa treatment[16] and an open trial of selegeline and L-Dopa[17] in a small patient group suggest that there may be a place for such therapy particularly in those cases where symptoms early in the disease resemble classical Parkinson's disease.

However, anti-Parkinsonian drugs may exacerbate confusion, hallucinations and behavioural symptoms and a balance may have to be struck between lucidity and immobility.

Multicentre collaboration to study the neurochemistry of LBD compared to AD with cortical LB has demonstrated that irrespective of diagnosis LBs are associated with greater cholinergic deficits. This has given rise to speculation on the future place of anticholinesterase inhibitors in the treatment of these patients. Encouraging early anecdotal reports, however, do not seem to have been borne out by subsequent experience.

Current theories

Several possible explanations have been postulated to explain the overlap between AD pathology and subcorti-

cal and cortical LB pathology. For example, it could be imagined that cortical and subcortical LB pathology lead to dementia when accompanied by chance by presymptomatic age-related Alzheimer pathology.[18] However, this seems less likely in view of recent quantitative evidence that AD pathology loading is greater in LB patients than in age matched normal controls. More in depth knowledge of the developmental sequence of pathology in AD confirms that the AD pathology in LB patients is 'early stage' and not simply age related.

Perhaps a common biological factor, eg. apoE-4 genotype, predisposes to the formation of both types of cortical pathology. Alternatively, it could be that the total number of neuronal inclusions is important and LBs represent modified neurofibrillary tangles such that either may reflect a common aetiological process of B amyloid deposition.[19]

Conclusion

Dementia associated with cortical LB is the second commonest cause of cognitive impairment in the elderly. Although increased awareness has been the first stage in understanding, many fundamental questions remain unanswered. What underlies neurofilament accumulation? Are LBs important pathological substrates causally related to neuronal loss? How does LB pathology and coincident AD pathology relate and which is responsible for the clinical dementia? Current data are based on small samples and there is clearly a need to establish pathological criteria for LBD and careful prospective clinical studies drawn from as representative a population as possible. Perhaps answers from these future investigations will help unravel the mystery and dispel the myth.

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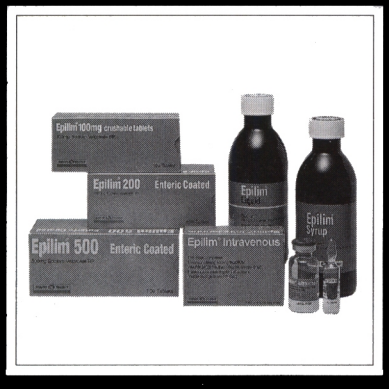

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