Advances in Psychiatric Treatment (1998), vol. 4, pp. 364–368

Commentary

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The article by Byrne gives a general overview of dementia with Lewy bodies (LBD) and discusses treatment in terms of modulation of neurotransmitter systems, treatment of psychotic symptoms and extrapyramidal features. However, as is the case with Alzheimer's disease, the dementia is related to underlying pathological processes which result in death and/or malfunction of neurons. Prevention or amelioration of this neuronal loss is therefore the ultimate aim of treatment. Such treatment is not yet available and the possibility of its development is likely to depend on further elucidation of the underlying pathological process. The relationship of LBD to Alzheimer's disease and Parkinson's disease should be considered, as this is important for the determination of the underlying pathological processes in LBD.

Molecular pathology of LBD

The principal pathological hallmark of LBD is the Lewy body, a spherical intracytoplasmic, eosinophilic, neuronal inclusion body 10–25 mm in diameter. The main constitutional protein is neurofilament with low, medium and high molecular weight forms. Several associated proteins such as ubiquitin and crystallin are also present. In LBD the Lewy bodies occur in specific vulnerable neurons in widespread areas of the brain. In the cerebral cortex Lewy bodies are found in small to medium-sized pyramidal neurons with higher densities in the deeper cortical layers. They occur in all association cortical areas but have a predilection for the temporal lobe, followed by frontal and parietal lobes, with lesser amounts in the occipital lobe. In the limbic lobe they occur in the entorhinal cortex, cingulate cortex, amygdala and hippocampus. In the hippocampus they occur almost exclusively in the subiculum but some CA1 forms have also been reported. They also occur in the nucleus basalis of Meynert, and various brain stem nuclei, such as pigmented cells in the pars compacta of the substantia nigra and the locus coeruleus. In addition to Lewy bodies extracellular amyloid deposits in the form of plaques, which in terms of morphology and distribution are indistinguishable from those in Alzheimer's disease (McKenzie *et al*, 1996), occur in practically all cases of LBD. Other pathological features of LBD include spongiform vacuolisation in the temporal lobe and the presence of Lewy-related neuritic changes which are prominent in the CA2 and CA3 regions of the hippocampus. Pathological changes in the pyramidal neurons of layers three and five of the cerebral cortex is more wide spread than indicated by Lewy body formation as many non-Lewy body containing neurons display a grainy appearance when labelled with an antineurofilament antibody (Smith *et al*, 1995). Computerised tomography scans demonstrate cerebral atrophy in LBD, this being most pronounced in the frontal lobes. As it is likely that Lewy bodies lead directly to malfunction and ultimately death of neurons, as suggested by the presence of extracellular Lewy bodies, this is likely to account for some of the cerebral atrophy. The dementia in LBD correlates with the density of Lewy bodies in the cerebral cortex, although granular changes in pyramidal neurons are also likely to contribute.

Relationship to Alzheimer's disease

The two main pathological lesions of Alzheimer's disease are amyloid plaques and neurofibrillary tangles (NFT). The amyloid plaques occur extracellularly and are composed of aggregates of a 40–

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42 amino acid peptide (β/A4-peptide) which is derived form the amyloid precursor protein (APP). NFTs are intraneuronal lesions consisting of aggregates of abnormally phosphorylated forms of the microtubular associated protein tau. The distribution of NFTs in the cerebral cortex and limbic lobe is similar to that of Lewy bodies. They occur in layer three and five pyramidal neurons in association cortical areas of the temporal, frontal and parietal lobes and to a lesser extent in the occipital lobe. In the limbic lobe they occur in the entorhinal cortex, CA1 of the hippocampus the subiculum and the amygdala. They also occur the nucleus basalis of Meynert and various brain stem nuclei such as the locus coeruleus. The vulnerable neurons for NFT formation would hence appear to be the same as those for Lewy body formation. An exception to this general rule, however, is an increased propensity for Lewy body formation in cells of the pars compacta of the substantia nigra and for NFT formation in the CA1 region of the hippocampus. NFTs do occur in the zona compacta cells in Alzheimer's disease but this tends to be late in the disease process (Reyes *et al*, 1996). This differential susceptibility of pars compacata cells for Lewy body formation could explain the early appearance of Parkinsonian features in LBD and their late appearance in Alzheimer's disease. The occurrence of Lewy bodies in LBD and NFTs in Alzheimer's disease is not absolute, as limbic NFTs occur in many cases of LBD and Lewy bodies can develop in the pars compacta cells in the later stages of Alzheimer's disease (Reyes *et al*, 1996). Also, the dual occurrence of NFTs and Lewy bodies, sometimes within the same neurons, has been reported in the amygdala in cases of Alzheimer's disease and LBD (Schmidt *et al*, 1996). Brain stem Lewy bodies have even been reported in early-onset autosomal dominant Alzheimer's disease due to a point mutation in the APP gene (Halliday *et al*, 1997). The distinction between the majority of LBD cases and Alzheimer's disease is, therefore, not clear. It is possible they could represent different manifestations of the same disease processes. In support of this apo E 4, a major genetic risk factor for Alzheimer's disease, is also associated with a similar increased risk for LBD (Galasko *et al*, 1995).

Relationship to Parkinson's disease

The most obvious pathological feature of Parkinson's disease is Lewy body formation and cell death of the pigmented dopamingeric neurons in the pars compacta of the substantia nigra. The pathology of Parkinson's disease, however, extends to many limbic structures and involves the entorhinal region, the CA2 sector of the hippocampus, anterior cingulate areas and the amygdala. These lesions in themselves are not associated with dementia and the 20% of people with Parkinson's disease who develop dementia usually have additional Alzheimer's disease pathology or Lewy body formation in the cerebral cortex. Some of the later cases could be classified as LBD, especially if the cerebral Lewy bodies are prominent and occur early in the disease progression. There is evidence to suggest that cortical Lewy bodies occur prior to brain stem Lewy bodies in LBD (Kosaka *et al*, 1996). An interesting recent finding is a point mutation (Ala53Thr) in the α-synuclein gene in four independent families with early-onset Parkinson's disease (Polymeropoulos *et al*, 1997). α-synuclein is a brain-specific protein thought to be involved in synapse formation and/or stabilisation. Initial interest in this protein was in relation to Alzheimer's disease, as a 35 amino acid peptide derived from this protein forms a minor part of amyloid in this disease. α-synuclein has now been shown to be present in brain stem and cortical Lewy bodies and Lewy body neurites in LBD and Parkinson's disease (Spillantini *et al*, 1997). Further evidence for a possible link between Parkinson's disease and LBD comes from the reported increased frequency of a CYP2D6B mutant allele in both diseases (Saitoh *et al*, 1995). The apo E ε4 allele, which is associated with both Alzheimer's disease and LBD, has not been reported to have an association with the dementia in Parkinson's disease (Marder *et al*, 1994).

Prospects for treatment

Further elucidation of the relationship between LBD and the associated neurodegenerative disorders Alzheimer's disease and Parkinson's disease is important in terms of determining the underlying pathological mechanisms. Once these mechanisms are unravelled avenues for treatment should be revealed. This is likely to be a long process, as despite the discovery of causative mutations in APP and the presenilin proteins plus a major susceptibility gene (apo E 4) in Alzheimer's disease, the mechanism of causation of this disease is still unknown.

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https://doi.org/10.1192/apt.4.6.364 Published online by Cambridge University Press

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Commentary

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Byrne provides an excellent clinical overview. However, I have selected four areas of clinical interest for more detailed consideration.

Psychiatric symptoms

All the studies in this area have identified visual hallucinations as a common symptom in LBD, occurring in a significantly higher proportion of patients with LBD compared with those with Alzheimer's disease. The prevalence rates of visual hallucinations do depend on the origin of the sample, occurring in 70% of patients from psychiatric cohorts and 20–30% of those in samples from neurological settings (Ballard *et al*, 1985).

Phenomenologically, these hallucinations are similar to those experienced by patients suffering from a wide variety of conditions including Parkinson's disease (Cummings, 1992) and the Charles Bonnet syndrome (Howard & Levy, 1994). Visual hallucinations are found to be more persistent (McShane *et al*, 1995; Ballard *et al*, 1997*a*) and also more severe in patients with LBD compared with sufferers of Alzheimer's disease (Ballard *et al*, 1995*a*). Other common psychotic symptoms in LBD include delusions, auditory hallucinations (Ballard *et al*, 1995*b*; Krzyminski, 1995) and delusional misidentification (Ballard et al, 1998*b*), all of which have higher prevalence rates than is seen in Alzheimer's disease.

Significant depression has been identified in 14–50% of patients with LBD (Klatka *et al*, 1996). There is insufficient evidence to suggest that depression is a helpful diagnostic discriminator, yet it is clear that it is a common occurence in patients with LBD and more information is needed about the effects, associations and outcome of depression in these individuals. Data from the Newcastle study (Ballard *et al*, 1997*b*) suggest a significant association with the severity of Parkinsonism, which would make intuitive sense given the high prevalence of depression among patients with Parkinson's disease.

Neuroleptic sensitivity reactions

McKeith *et al*'s (1992) series, reporting severe neuroleptic sensitivity reactions in LBD, had a huge impact upon clinical practice and was a

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