The Lewy body variant of Alzheimer disease

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Summary. The Lewy body variant of Alzheimer disease (LBV) occupies a messy middle ground between Alzheimer disease (AD) on the one hand, and pure Lewy body diseases (Parkinson's disease or diffuse Lewy body disease), on the other. In addition to brainstem and neocortical Lewy bodies, LBV brains have enough neocortical neuritic plaques to meet diagnostic criteria for AD. However, neurofibrillary pathology in LBV is modest, since tangle densities in LBV are typically intermediate between AD and age-matched controls or pure Lewy body disease brains. Apolipoprotein E-4 is overrepresented in LBV, as it is in AD but is not in PD or diffuse Lewy body disease (DLBD). Neurologically, LBV patients often display sufficient parkinsonian signs to separate them from AD, but these findings are usually too subtle to warrant clinical diagnoses of Parkinson's disease (PD). Neuropsychological deficits in LBV include a subcortical dementia pattern similar to DLBD, and more severe global cognitive impairment reminiscent of AD.

Introduction

The Lewy body variant of Alzheimer disease (LBV) is a clinical and pathologic entity (Hansen, 1990). LBV patients present during life with dementia, often with mild parkinsonian signs. At autopsy, LBV brains show subcortical and neocortical Lewy bodies, accompanied by sufficient numbers of neocortical senile plaques (both diffuse and neuritic) to meet widely accepted neuropathological criteria for Alzheimer disease (AD) (Khachaturian, 1985; Mirra, 1993).

The nomenclature of dementia associated with Lewy bodies is unsettled. Many cases which we designate as LBV would be labelled by other investigators as combined AD and PD (Ditter, 1987), AD with PD-related changes (Mirra, 1993), AD with incidental Lewy bodies (Joachim, 1988), AD with concomitant Lewy body disease (Hansen, 1989), senile dementia of the Lewy body type (Perry, 1990), diffuse Lewy body disease (DLBD), common form with plaques and/or tangles (Kosaka, 1990), or DLBD. We reserve the designation DLBD for the much smaller percentage of dementia brains with brainstem and neocortical Lewy bodies lacking accompanying neocortical...
AD pathology. Other investigators, however, make no such distinction (Dickson, 1987).

This nosologic tower of Babel results from differing underlying assumptions about whether LBV is primarily a form of AD with Lewy body flavouring, or fundamentally a type of Lewy body disease contaminated by non-specific age appropriate AD pathology. Such an issue is difficult to resolve, since most clinical, neuropsychological, and neuropathologic parameters place LBV squarely in-between AD and pure PD, or DLBD. This investigation describes the extent of AD neuropathology in LBV compared to pure DLBD and age-matched controls. We also review the clinical and neuropsychological characteristics of LBV patients compared to those with pure AD.

**Materials and methods**

*Subjects*

The neuropathologically characterized brains in this study came from patients prospectively evaluated at a number of sites associated with the Alzheimer’s Disease Research Center at the University of California, San Diego, over the past 10 years. Most of these patients carried the clinical diagnosis of probable or possible AD, and none were clinically diagnosed as Parkinson’s disease, although some had mild parkinsonian features. Non-AD, non-LBV, and non-DLBD control brains utilized for comparative purposes came from two groups. There were a small number of carefully examined cognitively intact elderly controls. A second group which we term “pathological controls”, came from clinically demented patients who at autopsy demonstrated non-AD, non-LBV and non-DLBD causes for dementia (e.g., multi-infarct dementia, progressive supranuclear palsy, or Pick’s disease).

*Specimen processing*

At autopsies, brains were removed in the usual fashion within 24 hours of death and divided sagittally while fresh. The left hemibrains were fixed in 10% buffered formalin while the right hemibrains were frozen at −70°C for chemical analysis. Following 10–14 days of fixation, the formalin fixed left hemibrains were weighed, examined externally, and sectioned. The calculated fixed whole brain weights were obtained by doubling the hemibrain values. Tissue blocks were taken from midfrontal cortex, superior temporal gyrus, inferior parietal cortex, anterior and posterior levels of the hippocampus, basal ganglia, substantia innominata, mesencephalon, and rostral pons. H&E stained sections 6–8 μm thick were prepared from these blocks. Sections 10 μm thick were stained with thioflavin-S and viewed with ultraviolet illumination and 440 μm bandpass wavelength excitation filters. After each neocortical section was surveyed to find areas with the most lesions, three X125 fields were counted for senile plaques, and three X500 fields for neurofibrillary tangles. The results were then averaged to provide single plaque and tangle counts for each neocortical region from every case. Neocortical senile plaque counts were subdivided into total and neuritic. Total plaques included both diffuse and neuritic varieties, and these counts were used for assigning cases to the AD and LBV categories based on National Institute on Aging (NIA) criteria (Khachaturian, 1985) which do not specify plaque type. Neuritic plaque frequencies were used for consigning