Common Inflammatory Mechanisms in Lewy Body Disease and Alzheimer Disease

Robert E. Mrak, MD, PhD and W. Sue T. Griffin, PhD

Abstract
Cortical Lewy body disease as a cause of dementia has been recognized for more than 40 years. Only in the past 15 to 20 years, however, has the true frequency of this entity come to be appreciated, primarily because of the advent of sensitive and specific immunohistochemical diagnostic techniques. We now know that there is frequent and extensive overlap, both clinically and pathologically, between Lewy body and Alzheimer diseases. Although some of this overlap may be attributable to common genetic and environmental risk factors, it is also now apparent that the 2 diseases share common neuroinflammatory mechanisms involving activation of microglia, overexpression of interleukin-1 and other inflammatory mediators, and inflammatory toxicity to neurons. Activated microglia are found in association with α-synuclein-containing neurons and glia in Parkinson disease, in dementia with Lewy bodies, and in multiple system atrophy, and these associations are reminiscent of microglial associations with neurofibrillary tangle-containing neurons in Alzheimer disease. In vitro and in vivo experimental work has shown reciprocal induction between α-synuclein and injured neurons on one hand and activated microglia and cytokine overexpression on the other. These neuroinflammatory processes may be a common link driving progression in both diseases and explaining the frequent overlap between the 2 diseases.

Key Words: α-Synuclein, Alzheimer disease, Dementia with Lewy bodies, Interleukin-1, Neuroinflammation, Parkinson disease.

INTRODUCTION
Cortical Lewy bodies were recognized as a substrate for clinical dementia as early as 1961 (1). Such “diffuse Lewy body disease,” however, was long considered to be a rare condition, with only about 30 such cases being reported over the next quarter century (2). By the mid-1990s, new immunohistochemical techniques greatly facilitated the recognition of cortical Lewy bodies, and cortical Lewy body disease became recognized as a relatively common cause of dementia. At this time it was also recognized that many (indeed, most) of these patients showed concurrent Alzheimer-type pathology (3). “Pure” Lewy body disease (without any Alzheimer-type pathology beyond that attributable to normal aging) is found in at most one third of Lewy body disease cases and thus represents perhaps 10% of all cases of clinical dementia. We, for instance, have found 31 cases of dementia with Lewy bodies among 202 autopsies for dementia (15%). These include 23 cases with concurrent Alzheimer disease (74% of Lewy body cases) and 8 cases without significant Alzheimer pathology (26% of Lewy body cases). Other large studies have returned similar results (reviewed in Reference 4).

This frequent and unexplained overlap between Alzheimer disease and dementia with Lewy bodies begs the question: What are the common etiologic or pathogenic factors at work in these 2 diseases that lead to such high rates of co-occurrence? Further, the occurrence of pure forms of each disease begs the additional question: What are the distinct etiologic or pathogenic factors that produce severe Alzheimer pathology with little or no Lewy body pathology in some patients and that produce severe Lewy body disease with little or no Alzheimer pathology in others?

GENETIC FACTORS UNDERLYING LEWY BODY DISEASE AND ALZHEIMER DISEASE: THE ROLE OF INTERLEUKIN-1 GENOTYPE
Alzheimer disease, Parkinson disease, and Lewy body dementia all occur in familial forms, and these familial forms have quite distinct genetic causes (5, 6). In addition, an as yet unidentified gene located on chromosome 12 has been associated with familial cases of Lewy body disease with concurrent Alzheimer disease (or the Lewy body variant of Alzheimer disease) (7).

For nonfamilial forms of these diseases, the ε4 allele of the apolipoprotein E gene (ApoE4) is overrepresented in Alzheimer disease and in cases of mixed Lewy body/Alzheimer disease but is underrepresented in cases of pure Lewy body disease (8). This suggests that ApoE4 may contribute to the appearance of Alzheimer-type neuropathologic changes in patients with Lewy body disease. Patients with Parkinson disease and dementia, without Alzheimer pathology, show normal representation of the ApoE4 allele (9), further supporting the association of the ApoE4 allele with Alzheimer-type changes. A number of additional genes have been associated with increased risk for late-onset Alzheimer disease (10, 11), but studies of these loci in...
regard to dementia with Lewy bodies are generally not available. The B allele of debrisoquine 4-hydroxylase (CYP2D6B; a cytochrome P-450 monoxygenase) has been found to be overrepresented in mixed Lewy body/Alzheimer disease by some (12) but not all investigators (13–15).

In contrast with the predominant association of ApoE4 with Alzheimer disease, genetic polymorphisms in the twin genes for interleukin (IL)-1α and IL-1β have been found to confer risk for both Alzheimer disease and Parkinson disease. These polymorphisms have not been studied in regard to dementia with Lewy bodies. We first showed increased risk for Alzheimer disease associated with certain polymorphisms in each of the 2 IL-1 genes, independent of the ApoE genotype (16, 17). The association of IL-1A polymorphisms with Alzheimer risk has been confirmed by 2 recent meta-analyses of ours and subsequent studies (18, 19). For Parkinson disease, several groups have shown increased risk associated with polymorphisms in the IL-1B gene (20–24), whereas no increased risk was found for IL-1A polymorphisms (22, 23, 25, 26). Although the implicated genetic loci for Alzheimer disease and Parkinson disease do not overlap, the common implication of IL-1 genotypes does focus attention on neuroinflammatory processes and, in particular, on microglial activation with IL-1 overexpression, as potential common pathogenic mechanisms for the 2 disorders.

ENVIRONMENTAL FACTORS UNDERLYING LEWY BODY DISEASE AND ALZHEIMER DISEASE

A number of environmental factors have been found to confer increased risk for Alzheimer disease (reviewed in Reference 27). There is a strong association with traumatic head injury, but risk is also conferred by many “lifestyle” factors long known to increase the risk of atherosclerotic cardiovascular disease. These include smoking, hyperlipidemia, hypertension, diabetes, and physical and mental inactivity. Of interest are several factors that have been associated with decreased risk for Alzheimer disease, such as use of antioxidants, anti-inflammatory agents (especially nonsteroidal anti-inflammatory agents), or lipid-lowering agents; postmenopausal hormonal replacement therapy; and moderate alcohol consumption. Inflammation is a common thread in many of these Alzheimer disease risk-enhancing conditions, and decreasing inflammatory processes, by measures mentioned above, are associated with protection.

For dementia with Lewy bodies, available epidemiologic studies of potential risk conferring environmental factors are limited. For Parkinson disease, however, there are studies suggesting increased risk associated with traumatic head injury (28) and decreased risk associated with use of nonsteroidal anti-inflammatory agents (29), with physical exercise (30), and with a diet rich in vitamin E (31). These latter findings echo epidemiologic findings for Alzheimer disease and, as is the case for Alzheimer disease, suggest a role for tissue injury and inflammatory responses in the pathogenesis of this form of Lewy body disease.

NEUROINFLAMMATION AS A COMMON PATHOGENIC FACTOR FOR LEWY BODY DISEASE AND ALZHEIMER DISEASE

Microglia-mediated neuroinflammatory processes are now well-established pathogenic components of Alzheimer disease and are thought to be key elements in driving lesion progression for both amyloid β plaques and neurofibrillary tangles. We first suggested in 1989 that a glial cytokine-mediated, neuroimmunologic process underlies the progression of Alzheimer-type neuropathologic changes and further suggested that this cytokine-mediated pathogenic driver might be a general phenomenon among chronic neurodegenerative disorders (32). We showed that amyloid β plaques contain activated microglia overexpressing IL-1, a potent immune response-generating cytokine (32, 33) and that such microglia are also found in association with neurofibrillary tangles (34). Since 1989, we have provided abundant evidence, based on human, animal, and cell culture studies, that IL-1, synthesized and released by activated microglia, is an important driving force in the transformation of diffuse amyloid deposits into neuritic amyloid β plaques as well as in the spread of these plaques and neuronal degeneration across regions of cerebral cortex in patients with Alzheimer disease. We have also provided evidence that IL-1 overexpression induces excessive tau phosphorylation and is related to tangle development in Alzheimer brain (35–37). These findings collectively offer strong evidence that the induction and overexpression of IL-1 could give rise to the full manifestation of Alzheimer pathology. These pathologic and experimental findings have thus anticipated and complemented epidemiologic and genetic studies linking neuroinflammation to Alzheimer risk.

α-Synuclein, a major constituent of Lewy bodies, is itself a potent activator of microglia and induces microglial expression of both IL-1 and tumor necrosis factor-α. Microglia stimulated by a combination of α-synuclein and interferon-γ are neurotoxic in vitro, and this effect is greater in the presence of mutant α-synucleins associated with familial Parkinson disease (38). Activated microglia are present in the substantia nigra of patients with Parkinson disease, where they express numerous cytokines and other inflammation-associated molecules (reviewed in References 39–41). In animal models of Parkinson disease, dopaminergic neuronal loss can be ameliorated by therapy with anti-inflammatory agents such as the peroxisome proliferator-activated receptor-γ agonist pioglitazone (42) or the selective cyclooxygenase-2 inhibitor celecoxib (43). In dementia with Lewy bodies there is a progressive association of microglia with degenerating Lewy body-containing neurons (44). Microglia are also found associated with α-synuclein-containing oligodendrocytes in human cases of multiple system atrophy (45) and in animal model of this disease (46). In patients with mixed Alzheimer disease and dementia with Lewy bodies, occasional neurons show simultaneous appearance of Lewy bodies and neurofibrillary tangles (47, 48). We have shown colocalization of IL-1-expressing microglia with such neurons (48) (Fig. 1).
CONCLUSIONS

Dementia with Lewy bodies and Alzheimer disease show frequent and extensive overlap, both clinically and pathologically. The 2 diseases share several genetic (polymorphisms in the genes for IL-1) and environmental (head injury, lesser use of nonsteroidal anti-inflammatory agents, physical inactivity, and a diet poor in vitamin E) risk factors that have in common increased neuroinflammatory states. Moreover, pathologic and experimental work has implicated the involvement of activated microglia and of microglia-derived IL-1 in the pathogenesis of the pathognomonic lesions of both diseases. Such neuroinflammatory processes may be a common link driving progression in both diseases and explaining the frequent overlap between the 2 diseases.

ACKNOWLEDGMENT

The authors thank Dr. Steve Barger for his review of the manuscript.

REFERENCES


