Dementia with Lewy bodies: Definition, diagnosis, and pathogenic relationship to Alzheimer's disease

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Abstract: Clinical dementia associated with the appearance of Lewy bodies in the cerebral cortex has been recognized for over 40 years. Until the 1990s, however, cortical Lewy body disease was thought to be a rare cause of dementia. At that time, the advent of sensitive and specific immunohistochemical techniques for highlighting these elusive structures led to the recognition of cortical Lewy body disease as a common substrate for clinical dementia. Current diagnostic criteria recognize dementia with Lewy bodies as a clinicopathological entity. Also recognized is the closely related (and perhaps biologically identical) entity of Parkinson's disease dementia, which differs from dementia with Lewy bodies only in the temporal sequence of appearance of clinical symptoms. The generic term "Lewy body disease" encompasses both entities. There is frequent and extensive overlap, both clinically and pathologically, between dementia with Lewy bodies and Alzheimer's disease. The two diseases share several genetic and environmental risk factors that have in common increased inflammatory states associated with increased disease risk. Moreover, pathological and experimental work has implicated the involvement of activated microglia and of microglia-derived interleukin-1 in the pathogenesis of the pathognomonic lesions of both diseases. Such neuroinflammatory processes may be the common link driving progression in both diseases and explaining the frequent overlap between the two diseases.

Keywords: dementia with Lewy bodies, Parkinson's disease, Alzheimer's disease, neuroinflammation, interleukin-1

Introduction

Dementia associated with Parkinson's disease has been long recognized. Approximately a third of Parkinson's patients develop dementia (and, conversely, approximately a third of Alzheimer patients show clinical evidence of parkinsonism) (Pollack and Hornabrook 1966; Liebermann et al 1979; Mosa et al 1984; Mayeux et al 1985; Perl et al 1998). Pathologically, there is also frequent and striking co-occurrence of Parkinson's disease with Alzheimer's disease, explaining at least in part the frequent occurrence of dementia in Parkinson's patients (Hakim and Mathieson 1979; Boller et al 1980). However, not all demented patients with clinically or pathologically defined Parkinson's disease show significant Alzheimer pathology, and dementia in many of these patients appears to be attributable to the occurrence of Lewy bodies within neurons of the cerebral neocortex.

The occurrence of Lewy bodies within the cerebral cortex of demented patients was recognized as early as 1961 (Okazaki et al 1961), and this was considered to be a true but rare cause of dementia. Only about 30 cases of such "diffuse Lewy body disease" were reported over the next quarter century (Burkhardt et al 1988). Most of these patients were not initially parkinsonian, but instead presented with dementia (and sometimes psychosis), and developed parkinsonian symptoms only later in their disease, if at all. The distinguishing pathological feature for this group of patients was the appearance

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of Lewy bodies (or "Lewy type" bodies) in neurons of the cerebral cortex. Unlike the classic Lewy bodies of Parkinson's disease, which are found in pigmented brainstem nuclei, these cortical Lewy bodies are only faintly eosinophilic, are not sharply demarcated by a surrounding halo, and do not show a radial filamentous substructure. All of these features made these cortical lesions difficult to identify, and thus made this disease difficult to diagnose. The wider recognition of cortical Lewy body disease was greatly facilitated by the development of sensitive immunohistochemical techniques in the late 1980s. Anti-ubiquitin antibodies were first found to reliably highlight Lewy bodies (Kuzuhara et al 1988; Lennox et al 1989); and antibodies against alpha-synuclein were subsequently found to be equally sensitive and much more specific (Spillantini et al 1987; Wakabayashi et al 1997).

By the mid-1990s cortical Lewy body disease was recognized as a relatively common cause of dementia. With the new immunohistochemical techniques, significant numbers of cortical Lewy bodies could be found in as many as 15%–25% of demented patients, although many of these patients also showed Alzheimer-type neuropathological changes. These latter changes, however, were generally restricted to neuritic plaque formation, with a paucity of accompanying neurofibrillary tangles. This combination of neuritic plaques and cortical Lewy bodies, without significant numbers of cortical neurofibrillary tangles, came to be known as the Lewy body variant of Alzheimer's disease (Hansen et al 1993). In 1995 a group of Lewy body disease specialists convened an international workshop on dementia with Lewy bodies, and issued consensus guidelines for clinical and pathological diagnosis (McKeith et al 1996). In addition to progressive (and often rapidly progressive) dementia, core clinical features that were identified were fluctuations in cognitive function, persistent well-formed visual hallucinations, and spontaneous motor features of parkinsonism. Criteria for pathological diagnosis were based on the number and distribution of Lewy bodies, with brainstem-predominant, limbic (transitional), and neocortical categories of Lewy body disease recognized. A distinction was made between "dementia with Lewy bodies" and "Parkinson's disease dementia", based solely on the temporal sequence of appearance of cognitive vs. motor symptoms.

These criteria were reviewed and modified by this same DLB Consortium in 2005 (McKeith et al 2005). At this time, greater diagnostic weight was given to symptoms and signs such as REM sleep behavior disorder, severe neuroleptic sensitivity, and reduced striatal dopamine transporter activity on functional neuroimaging. In addition, the criteria for pathologic diagnosis were modified: greater weight was placed on the anatomic distribution of Lewy bodies, and the final diagnosis was adjusted for concurrent Alzheimer-type neuropathological changes. Thus a given degree of Lewy body pathology might confer a "high likelihood" that the pathologic findings are associated with a DLB clinical syndrome in a patient with little or no Alzheimer-type changes, while the same degree of Lewy body might confer "intermediate" or even "low" likelihood of such association in the presence of extensive Alzheimer pathology. It should be noted that these latest pathological criteria thus moved away from the definition of Lewy body dementia as a disease, and toward the definition of Lewy body dementia as a clinicopathologic entity.

Clinical criteria for diagnosis of dementia with Lewy bodies

The 2005 report of the DLB Consortium (McKeith et al 2005) recognizes central, core, suggestive, and supportive features for the diagnosis of dementia with Lewy bodies. These features are then considered in light of other confounding clinical conditions and of the temporal sequence of appearance of cognitive and motor symptoms.

The central clinical feature of dementia with Lewy bodies is dementia. This should be of sufficient magnitude to interfere with normal social or occupational activities. Unlike Alzheimer's disease, memory impairment is not necessarily a prominent early feature, but this will usually appear with progression of the disease. Instead, deficits in attention, executive function, and visuospatial ability are often prominent early symptoms.

There are three core features for diagnosis. Two of these core features should be present for a diagnosis of *probable* dementia with Lewy bodies, while one core feature should be present for a diagnosis of *possible* dementia with Lewy bodies. The three core features are (1) fluctuating cognition with pronounced variation in attention and alertness, (2) recurrent visual hallucinations (typically well formed and detailed), and (3) spontaneous features of parkinsonism.

There are also three suggestive features for diagnosis. In the presence of one core feature, the additional finding of a suggestive feature justifies a diagnosis of probable dementia with Lewy bodies. In the absence of any core features, the presence of a suggestive feature justifies a diagnosis of possible dementia with Lewy bodies. The three suggestive features are (1) an REM sleep behavior disorder, (2) severe neuroleptic sensitivity, and (3) low dopamine transporter uptake in the basal ganglia demonstrated by SPECT or PET imaging.

Supportive features are often present, but are not sufficient for diagnosis. These include repeated falls and syncope; transient, unexplained loss of consciousness; severe autonomic dysfunction (eg, orthostatic hypotension, urinary incontinence), nonvisual hallucinations, systematized delusions, depression, relative preservation of medial temporal lobe structures on CT or MRI scans, generalized low uptake on SPECT/PET perfusion scans with low occipital activity, abnormally low uptake on MIBG myocardial scintigraphy, and prominent slow wave activity on EEG with temporal lobe transient sharp waves.

These diagnostic criteria are considered in light of other confounding clinical conditions. Thus, a diagnosis of dementia with Lewy bodies is less likely in the presence of clinical or imaging evidence of cerebrovascular disease, in the presence of other clinical conditions that might explain the clinical findings, and if parkinsonism appears only as a late complication in a severely demented patient.

Finally, the diagnostic distinction is made between Parkinson disease dementia and dementia with Lewy bodies is retained from the 1996 criteria. As noted above, this distinction is based solely on the temporal sequence of appearance of cognitive and motor symptoms. This distinction was retained in the revised 2005 criteria for the sake of uniformity in clinical research studies. The members of the consortium recognized, however, that this distinction is not always possible in clinical settings, and for such situations they recommend the generic term "Lewy body disease".

Pathological criteria for the diagnosis of dementia with Lewy bodies

The same 2005 report of the DLB consortium (McKeith et al 2005) also defined pathological criteria for the postmortem diagnosis of dementia with Lewy bodies. Lewy bodies are sought in ten well defined anatomic areas of the brain, using specific immunohistochemical methods. These are then assessed for frequency using a semi-quantitative visual method, rather than actual counting of Lewy bodies. Based on the distribution and frequency of Lewy bodies, the patient is assigned to one of three stages (or "types") of Lewy body disease: brainstem-predominant (corresponding to classic Parkinson's disease), limbic or transitional (a self-explanatory stage), and diffuse neocortical (which corresponds to the earlier reports of diffuse cortical Lewy body disease). There is then an assessment made of the "likelihood" that the pathological findings explain, or "are associated with," clinical dementia.

This assessment takes into account the presence and extent of concurrent Alzheimer-type neuropathological changes, with Lewy body pathology judged "more likely" to explain the dementia in the presence of little or no Alzheimer pathology, and "less likely" to explain the dementia in the presence of more extensive Alzheimer changes.

The anatomic areas employed for the postmortem diagnosis of dementia with Lewy bodies include the three brainstem nuclei (the nuclei for cranial nerves IX and X, the locus coeruleus, and the substantia nigra), three basal forebrain/limbic areas (amygdala, transentorhinal cortex, and cingulate gyrus), and three neocortical areas (frontal, parietal and temporal cortex). The brainstem nuclei are those classically involved in Parkinson's disease, and are the first areas in the brain in which Lewy bodies appear (Braak et al 2003). The forebrain/limbic and neocortical areas reflect the further patterns of Lewy body disease progression defined by Braak et al (2003). Progressive involvement of these areas has been shown to correlate with deteriorating function on the Mini-Mental State Examination (MMSE) (Braak et al 2005). The frontal, parietal and temporal neocortical areas to be examined are identical to those used by CERAD criteria and by NIH-Reagan guidelines for the pathological diagnosis of Alzheimer's disease (Mirra et al 1991; NIH 1997).

The most specific immunohistochemical method for the detection of Lewy bodies employs antibodies to alpha-synuclein. Anti-ubiquitin antibodies will also detect Lewy bodies, but this technique also highlights Alzheimer-type neurofibrillary changes, and thus is less useful in cases with co-existent Alzheimer pathology. As noted above, cortical Lewy bodies (unlike brainstem Lewy bodies) are subtle on routine H&E staining, making them difficult to recognize and almost impossible to quantify without immunohistochemistry.

The frequency of Lewy bodies in the various anatomic areas examined is assessed on a 5-point semi-quantitative scale, based on the following approximate numbers of Lewy bodies (LB) per low power (100X) microscopic field: stage 0 'no Lewy bodies; stage 1 = <1 LB; stage 2 = 2-3 LBs; stage 3 = ≥4 LBs; and stage 4 = numerous (>20) LBs. The type of Lewy body disease is then assigned based on the LB scores in the nine areas assessed: brainstem predominant Lewy body disease shows high LB scores in brainstem nuclei, low scores in forebrain/limbic areas, and no LBs in neocortical areas; limbic (transitional) Lewy body disease shows high LB scores in brainstem nuclei, intermediate or high LB scores in forebrain/limbic areas, and low LB scores in neocortical areas; and diffuse neocortical Lewy body disease shows

high LB scores in brainstem and forebrain/limbic areas and intermediate or high LB scores in neocortical areas.

The likelihood of Lewy body-associated clinical dementia is then assessed based on both the type (stage) of Lewy body pathology present and the extent of concurrent Alzheimer pathology. Greater Lewy body pathology (higher types) confer greater likelihood, while greater degrees of Alzheimer pathology (based on the stageing system of Braak and Braak, 1991) confer lesser likelihood. Thus, there is low likelihood that brainstem-predominant Lewy body disease is associated with clinical dementia, regardless of the extent of Alzheimer pathology. There is high likelihood that neocortical Lewy body disease is associated with clinical dementia, unless there is also severe (Braak and Braak stage V or VI) concurrent Alzheimer pathology, in which case the likelihood is intermediate. For limbic (transitional) Lewy body disease, the likelihood of association with clinical dementia is high in the absence of significant Alzheimer pathology (Braak and Braak stages 0-II), low in the presence of severe Alzheimer pathology (Braak and Braak stages V or VI), and intermediate with intermediate Alzheimer pathology (Braak and Braak stages III or IV).

Overlap between dementia with Lewy bodies and Alzheimer's disease

As noted above, co-occurrence of Alzheimer's disease and Lewy body disease (or of Alzheimer's disease and Parkinson's disease) is common, and this has long been recognized. Indeed, the simultaneous appearance of Lewy bodies and Alzheimer neurofibrillary tangles within the same neuron was recognized as early as 1978 (Forno et al 1978). The overlap between these two diseases is so extensive that "pure" Lewy body disease (without any Alzheimer-type pathology beyond that attributable to normal ageing) is relatively uncommon, accounting for no more than a third of all cases of Lewy body disease and at perhaps 10% of all cases of clinical dementia. In our experience with 202 autopsies of demented individuals, for instance, we found 31 cases of dementia with Lewy bodies (15% of demented individuals), including 23 cases with concurrent Alzheimer's disease and 8 cases without significant Alzheimer pathology. "Pure" dementia with Lewy bodies thus represented 4% of all dementia cases (8/202) and 26% of all Lewy body cases (8/31) in our series. Other large studies have found Lewy body disease in 14%–26% of demented patients, and have found "pure" Lewy body disease in 0%–19% of demented patients (reviewed by Barker et al 2002).

The frequent and unexplained overlap between Alzheimer's disease and dementia with Lewy bodies begs the question: What are the common etiologic or pathogenic factors at work in these two disease that lead to such high rates of co-occurrence? 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's disease

Alzheimer's disease, Parkinson's disease, and Lewy body dementia all occur in familial forms, and these familial forms have quite distinct genetic causes (Graeber and Mueller 2003; Bortoli-Avella et al 2004). In addition, an as-yet-unidentified gene located on chromosome 12 between D12S373 and D12S390 has been associated with familial cases of Lewy body disease with concurrent Alzheimer disease (or Lewy body variant of Alzheimer disease) (Scott et al 2000).

For the more common, non-familial, late-onset variants of Alzheimer's disease, the ε4 allele of the apolipoprotein E gene (ApoE4) has been found to confer significant risk. Interestingly, this allele is also overrepresented in cases of mixed Lewy body/Alzheimer's disease, but underrepresented in cases of pure Lewy body disease (Galasko et al 1994). This suggests that ApoE4 may contribute to the appearance of Alzheimer-type neuropathological changes in patients with Lewy body disease. Patients with Parkinson's disease and with dementia, but without Alzheimer pathology, show normal representation of the ApoE4 allele (Benjamin et al 1994), 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's disease (Kamboh et al 2004; Seretti et al 2005), 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's disease by some (Saitoh et al 1995), but not by others (Bordet et al 1994; Atkinson et al 1999; Furuno et al 2001).

Genetic polymorphisms in the twin genes for interleukin-1alpha and interleukin-1beta (IL-1A and IL-1B) have been found to confer risk for both Alzheimer's

disease and Parkinson's disease; these polymorphisms have not been studied in regard to dementia with Lewy bodies. For Alzheimer's disease, we first showed increased risk for Alzheimer's disease associated with certain polymorphisms in both genes, independent of ApoE genotype (Grimaldi et al 2000; Nicoll et al 2000). Two recent meta-analyses of this and subsequent studies have confirmed a small but significant elevation of risk associated with IL-1A genotype (Combarros et al 2004; Rainero et al 2004). For Parkinson's disease, increased risk has been associated with polymorphisms in the IL-1B gene (Nishimura et al 2000, 2005; Mattila et al 2002; McGeer et al 2002; Schulte et al 2002) but not the IL-1A gene (Dodel et al 2001; McGeer et al 2002; Schulte et al 2002; Moller et al 2004). While the implicated genetic alleles for Alzheimer's disease and Parkinson's disease thus do not overlap, the common implication of interleukin-1 genotypes does focus attention on inflammatory processes as potential common pathogenic mechanisms for the two disorders.

Environmental factors underlying Lewy body disease and Alzheimer's disease

Over the past few decades a number of environmental factors have been found to confer increased risk for Alzheimer's disease (reviewed by Mayeaux 2003). Traumatic head injury is a major environmental risk factor, but risk is also conferred by many factors also known to increase the risk of atherosclerotic cardiovascular disease; these include smoking, hyperlipidemia, hypertension, and diabetes. Factors that decrease risk for Alzheimer's disease include active physical and mental activity (especially in late life), and use of antioxidants, anti-inflammatory agents (especially non-steroidal anti-inflammatory agents, or NSAIDs), lipid-lowering agents, and post-menopausal hormonal replacement. Moderate consumption of alcohol has also been shown to be protective. A common thread of many or these factors is an increase in inflammatory processes associated with increased risk, and a decrease in inflammatory processes associated with protection.

Studies on the environmental epidemiology of dementia with Lewy bodies are not yet available. For Parkinson's disease there are a number of studies suggesting that both cigarette smoking and coffee consumption are associated with decreased risk, although the mechanisms involved and the biological significance of these findings are not yet clear (see Hernan et al 2002). More intriguing are studies

suggesting increased risk of Parkinson's disease associated with traumatic head injury (Bower et al 2003), and protection against Parkinson's disease associated with use of NSAIDs (Chen et al 2003), with physical exercise (Chen et al 2005), and with a diet rich in vitamin E (but not with vitamin E supplementation) (Zhang et al 2002). These latter findings echo similar results in epidemiological studies of Alzheimer's disease and, as is the case for Alzheimer's disease, suggest a role for tissue injury and inflammatory responses in the pathogenesis of this disease.

Neuroinflammation as a common pathogenic factor for Lewy body disease and Alzheimer's disease

We first suggested in 1989 that a glial cytokine-mediated, neuroimmunological process underlay the progression of Alzheimer-type neuropathological changes. This was based on our demonstration that activated microglia overexpressing interleukin-1 (IL-1), a potent immune response-generating cytokine, and activated astrocytes overexpressing S100B, a cytokine that promotes excessive neurite growth, in Alzheimer's disease (Griffin et al 1989). These activated glia are found in association with both Aβ plaques (Griffin et al 1995) and neurofibrillary tangles (Sheng et al 1997). 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 Aβ plaques (Griffin et al 1989) as well as in the spread of these plaques and neuronal degeneration across regions of cerebral cortex in Alzheimer patients (Sheng et al 1995). We have also provided evidence that IL-1 overexpression induces excessive tau phosphorylation, and is related to tangle development in Alzheimer brain (Sheng et al 2000, 2001; Li et al 2003). These findings collectively offered strong evidence that the induction and overexpression of IL-1 could give rise to the full manifestation of Alzheimer pathology.

At that time of our initial report in 1989, we also suggested that this cytokine-mediated process could be generalized to other chronic, neurodegenerative disorders. We have recently shown that IL-1β, produced by microglia activated in response to neuronal stress, promotes neuronal expression of the Lewy body protein α-synuclein, as well as the Alzheimer neurofibrillary tangle-associated protein phosphorylated tau, concomitant with decreased expression of the synaptic protein synaptophysin (Griffin et al 2006). These effects were demonstrable both in vivo, in glial-neuronal

co-culture systems, and in vivo, in rats intracerebrally implanted with slow-release, IL-1-containing pellets. We also showed colocalization of IL-1-expressing microglia with neurons that simultaneously contained both Lewy bodies and neurofibrillary tangles in human cases of mixed Alzheimer/Lewy body disease.

These findings provide a mechanistic link between neuronal stress, microglial activation, IL-1 overexpression, and IL-1-driven events, leading to the recognized neuropathological changes that encompass both Alzheimer's disease and Parkinson's disease. IL-1-mediated downstream consequences may favor manifestations or precocious development of Alzheimer's disease, Parkinson's disease, or Alzheimer's disease/Lewy body disease, a distinction likely dependent on the originating insult or the specific neuronal cell type first affected, although the nature of such insults remain largely unknown for both Alzheimer's disease and Lewy body disease.

Conclusion

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

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