Journal of the International Neuropsychological Society (1997), **3**, 179–194.

CRITICAL REVIEW

Lewy bodies and progressive dementia: A critical review and meta-analysis

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(RECEIVED November 15, 1995; ACCEPTED January 30, 1996)

Abstract

Researchers disagree as to whether Lewy body disease (LBD) constitutes a variant of Alzheimer's (AD) or Parkinson's disease (PD), or alternatively, whether it is an independent disease process. The neuropathological, genetic, and clinical characteristics of LBD are reviewed and compared to those of AD and PD. Data for 150 cases of LBD reported in the literature were compiled and grouped according to neuropathological status. Patients with pure LBD (with limited or no concurrent AD pathology) tend to present at a younger age with extrapyramidal signs followed by dementia, whereas patients with mixed LBD–AD (concurrent LB and AD pathology) are somewhat older and tend to present with dementia. The cognitive profile of LBD patients, and the relationships among LBD, AD, and PD remain unclear due to methodological limitations and the paucity of studies comparing the groups directly. (*JINS*, 1997, *3*, 179–194.)

Keywords: Lewy body disease, Alzheimer's disease, Parkinson's disease, Clinicopathological correlates

INTRODUCTION

Fritz Heinrich Lewy (1912, 1923), a contemporary of Alois Alzheimer, first reported the neuronal inclusion body that bears his name, the Lewy body (LB), in 1912. Hassler (1938), and later Woodard (1962), subsequently described what appeared to be a distinct clinical syndrome associated with cortical LBs. The syndrome was characterized by an insidious onset, usually after age 50 years, of affective disorder, delusions, or severe behavioral disturbance, with memory and intellectual impairment developing later (Woodard, 1962). Widespread interest in cortical LBs and their associated clinical syndrome, referred to as Lewy body disease (LBD), emerged only about 10 to 12 years ago (Yoshimura, 1983; Gibb et al., 1985; Dickson et al., 1987), and has accelerated dramatically since.

Recent debate regarding LBD has centered on nosology. Numerous diagnostic labels have been proposed for this syndrome, including diffuse Lewy body disease (Byrne et al., 1989; Lennox et al., 1989; Kosaka, 1990), senile dementia of the Lewy body type (Perry et al., 1990), the Lewy body variant of Alzheimer's disease (Hansen et al., 1990), and Parkinson's disease in Alzheimer's disease (Ditter & Mirra, 1987). This variation in labeling reflects the scope of disagreement regarding the classification of LBD. Ultimately, the classification of LBD will depend upon whether it is determined to be a variant in the Alzheimer's disease (AD) spectrum, Parkinson's disease (PD) spectrum, or constitutes a disorder independent of AD and PD. Tables 1 and 2 summarize comparative neuropathological and clinical data, respectively, for LBD, AD, and PD, as extracted from the literature.

The proportion of patients with a clinical diagnosis of dementia (often AD) who later were found to meet neuropathological criteria for a diagnosis of LBD has recently been estimated at 20 to 30% (Perry et al., 1989; Hansen et al., 1990). If accurate, this would make LBD the second most common cause of dementia after AD. Thus, the implications for the accurate clinical identification of LBD become obvious.

Terminology

Kosaka (1990) distinguished between "common" and "pure" forms of LBD. The majority of reported cases of LBD are of the common form, which is characterized by (1) numerous LBs distributed throughout the neocortex, diencephalon, brainstem, and basal ganglia, and (2) sufficient amyloid

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Table 1. Comparative neuropathology in clinically defined normal aging, Alzheimer's disease, Lewy body disease, and Parkinson's disease

Pathology	Normal aging	AD	Mixed LBD	AD+PD	Pure LBD	PD w/dementia	PD w/o dementia
Diffuse AP	Variable	WD; esp. FAC, PTP, MTG, ITG, Amyg	Similar to AD; exact distribution unknown	Similar to AD; exact distribution unknown	Variable; distribution unknown	WD	Variable
Neuritic AP	Rare/absent	WD; esp. FAC, PTP, MTG, ITG, Amyg	Possibly fewer than in AD; distribution unknown	Possibly fewer than in AD; distribution unknown	Few; distribution unknown	WD; fewer than in AD or LBD	Few/absent
NFT	Few in CA1, Sub, ERC; Rare in neocortex and brainstem	WD; esp. in FAC, PTP, PCG, ERC, Sub, CA1, Amyg	Variable; distribution unknown	Variable; when present, similar to AD, but fewer in ERC and CA1	Few	WD; fewer than in AD or LBD	Few/absent
Neurites/ neuropil threads	Variable	WD; few/absent in CA2–3	WD; including CA2–3, but fewer than in pure LBD	WD; including CA2–3, but fewer than in pure LBD	CA2–3 > CA1; few/absent in neocortex	WD; fewer than in AD or LBD	Absent
Spongiform vacuolation	Rare/absent	Variable in temporal neocortex	Temporal neocortex, more common than in AD	Temporal neocortex, more common than in AD	STG, ERC, Amyg	Absent	Absent
LB	Few in LC; fewer in SN, DVN; rare in Hyp, NBM, neocortex	Few/variable, typically restricted to SN	SN, LC, Hyp, NBM, DVN; variable in ERC, TNC, ACG, insula	SN, LC, Hyp, NBM, DVN; variable in ERC, TNC, ACG, insula	SN, LC, Hyp, NBM, DVN; WD in neocortex, esp. ERC, TNC, ACG, FAC, insula	SN, LC, Hyp, NBM, DVN; variable in neocortex	SN, LC, Hyp, NBM, DVN; ERC, ACG, variable in insula

This table is not intended to be exhaustive, rather to highlight differences between diagnostic groups. ACG = anterior cingulate gyrus, AD = Alzheimer's disease, Amyg = amygdala, AP = amyloid plaque, CA1 = hippocampal CA1 region, CA2–3 = hippocampal CA2–3 region, DVN = dorsal vagal nucleus, ERC = entorhinal cortex, FAC = frontal association cortex, Hyp = hypothalamus, ITG = inferior temporal gyrus, LB = Lewy body, LBD = Lewy body disease, LC = locus ceruleus, MTG = middle temporal gyrus, NBM = nucleus basalis of Meynert, NFT = neurofibrillary tangle, PCG = posterior cingulate gyrus, PD = Parkinson's disease, PTP = posterior temporoparietal cortex, SN = substantia nigra, STG = superior temporal gyrus, Sub = subiculum, TNC = Temporal neocortex, WD = widely distributed.

plaques (APs) or neurofibrillary tangles (NFTs) to meet neuropathological criteria for AD (Khachaturian, 1985; Mirra et al., 1991). Pure LBD is characterized neuropathologically by (1) LBs distributed throughout the cerebral cortex, with greater numbers in specific predilection sites (described below); and (2) little or no concomitant AD pathology.

This paper will review the literature on clinicopathological correlates of common and pure LBD and the relationship of these to AD and PD. The disease-related terms used in this review are either those invoked by the authors of case reports themselves, or for the purposes of consistency and clarity, a substitute term that is descriptive of the disease and consistent with the intent of the original author(s). The present review makes no attempt to endorse any prevailing view of the pathogenesis of LBD. Rather, it strives to present and critique all arguments regarding the etiology and clinical correlates of LBD. Following the literature review, a meta-analysis of the clinical features of 150 reported cases of neuropathologically diagnosed LBD is presented. This analysis is intended to consolidate the LBD literature, and to present data that may support or refute current hypotheses regarding the clinical characteristics of LBD.

LEWY BODY DISEASE AND THE PARKINSON'S DISEASE SPECTRUM

Comparative Histopathology

Based on histopathological similarities, some investigators consider LBD to represent a subtype within the PD spectrum (Hughes et al., 1993; Sugiyama et al., 1994). Classically, LBs have been considered to be the pathognomonic lesion in idiopathic PD. The typical distribution of LBs in PD involves the substantia nigra (SN), locus coeruleus (LC), substantia innominata, nucleus basalis of Meynert (NbM), dorsal vagal nucleus, and hypothalamus (Gibb et al., 1985; Jellinger, 1986; Hansen & Galasko, 1992; Sandyk & Willis, 1992). In addition, numerous LBs are present in the neocortex of patients with LBD (more than 5 per 100× field; Kosaka, 1990), and are particularly concentrated in the anterior cingulate gyrus, insula, frontal neocortex, and temporal neocortex. However, LBs are typically not found in the hippocampus, and are infrequent in the subiculum (Gibb et al., 1985). Importantly, no LBD patients have been identified as having cortical LBs without subcortical LBs, al-

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Table 2. Summary of comparative clinical and genetic data in AD, LBD, and PD

Variable	AD	Mixed LBD	Pure LBD	PD
Age at onset (years)	Early to middle eighth decade	Middle seventh decade	Early to middle seventh decade	Middle sixth decade
Disease duration (years)	$M \cong 10$	$M \cong 6$	$M \cong 6$	Variable: early-onset $M \cong 14$–18; late-onset $M \cong 6$–8
Sex ratio (M:F)	Nearly 1:1, slightly higher in women	Unknown; possibly higher in men	Unknown; possibly higher in men	Between 2:1 and 3:2
Prevalence of dementia	100%	Approaching 100%	Unknown; probably approaching 100%	10–40%
Presenting symptoms	Typically memory impairment	Typically memory impairment; neuropsychiatric symptoms	Extrapyramidal signs and/or memory impairment	Extrapyramidal signs, depression
Extrapyramidal signs	Appears late if at all; associated with nigral LBs	Appears early, usually after dementia; predominantly rigidity/bradykinesia	Appears early; predominantly rigidity/bradykinesia	Classic motor triad
EEG	Normal early, posterior background slowing then diffuse slowing later	Often abnormal early; background slowing with high frequency frontal bursts	Often abnormal early; background slowing with high frequency frontal bursts	Generalized slowing, greater in PD with dementia than PD without dementia
ApoE allele status	Increased $\epsilon 4$ prevalence	Increased $\epsilon 4$ prevalence	$\epsilon 4$ prevalence equivalent to normal elderly	$\epsilon 4$ prevalence equivalent to normal elderly
Psychopathology	40–50%, typically 3–4 years post-onset: delusions, followed by hallucinations	May be early and prominent; prevalence may be higher than in AD	May be early and prominent; prevalence may be higher than in AD	Depression, 40–60%
Symptom fluctuation	5–20%	Unknown, reported at 50–90%	Unknown, reported at 50–90%	Not reported
Neuropsychological profile	Cortical dementia	Possibly combined cortical–subcortical dementia	Possibly combined cortical–subcortical dementia	Subcortical dementia; nondemented PD show impaired construction and verbal fluency

though one reported case was characterized by milder SN involvement relative to cortical involvement (Ikeda et al., 1980). Patients with LBD show a similar subcortical distribution of LBs to patients with PD. Although 75% to 100% (Perry et al., 1991; Hughes et al., 1992; Hughes et al., 1993; Sugiyama et al., 1994) of PD patients also are reported to have cortical LBs, they are typically less abundant than in LBD patients, and are restricted to limbic and insular cortices (Pollanen et al., 1993).

Recent research has revealed several important histopathological differences between LBD and PD. Hughes et al. (1993) found additional non-PD pathology (Alzheimer-type, vascular, numerous cortical Lewy bodies) in 45% of PD patients who developed dementia. Dementia in PD patients appears to be more strongly associated with the number of neocortical Lewy bodies (Zweig et al., 1993; Sugiyama et al., 1994), neuronal loss in the LC and NbM (Zweig et al., 1993), and greater numbers of APs and NFTs (Paulus & Jellinger, 1991; cf. Daniel & Lees, 1991) than to PD-specific pathology (i.e., brainstem LBs and cell loss). However, the extent to which each of these neuropathological factors contributes independently to the likelihood of developing dementia in PD is unknown.

Comparative Clinical Characteristics

Clinically, the major similarities between PD and LBD are the presence of extrapyramidal signs (EPS) and dementia. All PD patients have some form of EPS, most commonly the triad of resting tremor, rigidity, and bradykinesia. In addition, there are often disturbances in station (e.g., stooped posture) and gait (e.g., shuffling, festination, retropulsion). In pure and common LBD patients, EPS seem to be milder (Hansen et al., 1990), and the prevalence of EPS may be lower than in PD patients (Gibb et al., 1989; Kosaka, 1990). Rigidity and bradykinesia tend to predominate over tremor in both pure and common LBD patients (Byrne et al., 1989; Crystal 1990; Kosaka, 1990).

The prevalence of dementia in PD is reported to range between 9 and 20% (Brown & Marsden, 1984; Rajput et al., 1984; Mayeux et al., 1988). Two recent population-based studies found prevalence rates of 18% (Tison et al., 1995) and 40% (Mayeux et al., 1992), respectively. In contrast, although the prevalence of dementia in patients with neuropathologically diagnosed LBD has not yet been definitively determined, several clinical series suggest it approaches 100% (Gibb et al., 1985; Burkhardt et al., 1988;

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Byrne et al., 1989; Hughes et al., 1993). Our review of the literature revealed rare cases of neuropathologically diagnosed LBD with no evidence of dementia (Ikeda et al., 1978; Lippa et al., 1994, Case Number 9) or EPS (Lippa et al., 1994).

PD patients with a predominantly akinetic or rigid clinical presentation may be at higher risk to develop dementia than those with predominant tremor (Ebmeier et al., 1991; Huber et al., 1991; Hughes et al., 1993). Significantly fewer PD patients with an excellent initial response to levodopa treatment later developed dementia, compared to patients with little or no response (Portin & Rinne, 1984; Hughes et al., 1993). Two PD patients who showed prominent akinesia and a poor response to levodopa treatment were found to have numerous LBs in the limbic cortices at autopsy (Mark et al., 1992). These data suggest that variability in patients with clinically diagnosed PD may result from a spectrum of neuropathology ranging from exclusive brainstem LB pathology to diffuse cortical LB pathology (see Kosaka et al., 1980).

In PD, EPS always precedes the onset of dementia. In LBD, presenting symptoms may vary according to the extent of AD-type pathology. In common LBD, the onset of cognitive impairment often precedes, or co-occurs with the onset of EPS (Burkhardt et al., 1988; Gibb et al., 1989; McKeith et al., 1992). In pure LBD, EPS tend to be the presenting sign with dementia occurring later, much as in PD (Byrne et al., 1989; Kosaka, 1990). It is not known if the interval between the onset of EPS and the onset of dementia differs in PD and pure LBD.

The relationships in PD among age at onset of illness, duration of illness, and age at onset of dementia are not yet well delineated. Some studies have found a correlation between the age at onset of dementia and duration of illness in PD (e.g., Rajput et al., 1984). However, most studies suggest that age at onset of dementia in PD appears to be independent of the duration of illness, and is probably more closely related to the chronological age of the patient (Portin & Rinne, 1984). In early-onset PD patients (age 60 years or younger), the mean disease duration prior to the onset of dementia was about 14 years; in late-onset PD patients (older than 60 years), disease duration prior to the onset of dementia was about 7 years (Hughes et al., 1993). Similarly, several other studies have found that dementia is more common among PD patients who are older at the time of illness onset (Reid et al., 1989; Marder et al., 1990; Ebmeier et al., 1991; Marder et al., 1991). In a population-based study, demented PD patients were significantly older than nondemented PD patients, but disease duration was equivalent (Mayeux et al., 1992). These findings suggest that dementia in PD is more closely related to the patient's age rather than to the duration of illness. However, it should be noted that some studies finding a relationship between age at dementia onset and chronological age, but not disease duration, fail to account for the differential mortality between PD patients with and without dementia and normal control individuals, which may result in spuriously low correlations between age at dementia onset and illness duration.

Unfortunately, no studies have compared the cognitive functioning of patients with LBD to those with PD. Demented PD patients show deficits in multiple domains of cognitive functioning, including language, visuospatial and constructional abilities, learning and memory, and executive abilities (Brown & Marsden, 1990; Mahurin et al., 1993). Furthermore, *nondemented* PD patients show deficits in verbal fluency, visuospatial ability (Stern et al., 1993; Jacobs et al., 1995), and in particular, executive abilities, as demonstrated on the Wisconsin Card Sorting Test (Lees & Smith, 1983; Brown & Marsden, 1988), Stroop Test (Brown & Marsden, 1991), and performance in dual-task paradigms (Brown & Marsden, 1991; Dalrymple-Alford et al., 1994). In contrast, language and memory appear to be largely unaffected in nondemented PD patients (Caltagirone et al., 1989). Comparison of the neuropsychological profiles of patients with PD and LBD awaits investigation.

Overall, convergent evidence suggests that the pathological mechanism of PD may not necessarily be associated with the development of frank dementia in PD patients. While PD and LBD patients share a common neuropathological lesion, the LB may represent a final common pathway associated with two distinct mechanisms. Alternatively, LBD may represent a phenotypic variant of PD involving the generalization of LB pathology within the brain. The factors that may contribute to LB generalization, however, are unknown.

LEWY BODY DISEASE AND THE ALZHEIMER'S DISEASE SPECTRUM

Comparative Neuropathology

The current debate regarding LBD nosology focuses on whether LBD constitutes a phenotypic variant of AD (Hansen & Galasko, 1992; Edwards et al., 1993; Förstl et al., 1993). Considerable neuropathological evidence exists to support the position that LBD is a variant of AD. A central neuropathological feature of AD is the abnormal deposition of beta-amyloid protein (β-AP) in the brain. Common LBD and AD patients appear not to differ in the total amount of cerebral β-AP (Gentleman et al., 1992) or overall number of amyloid plaques (Lippa et al., 1994). AD and all LBD patients show significant neuronal loss in the NbM (Pollanen et al., 1993). In addition, a familial case of AD known to result from a mutation in the amyloid precursor protein gene met histopathological criteria for both LBD and AD (Lantos et al., 1992). However, this mutation does not account for the majority of AD cases (Murrell et al., 1991; Clark & Goate, 1993), and may not necessarily be the source of LB pathogenesis.

Despite these commonalities, there are important neuropathological differences between AD and LBD patients. AD patients have two main types of AP: diffuse plaques, which are immunoreactive only to β-AP and ubiquitin, and neuritic plaques, which are immunoreactive not only to β-AP

https://doi.org/10.1017/S1355617797001793 Published online by Cambridge University Press

and ubiquitin, but often (although not always) to tau protein as well. Patients with pure LBD have almost exclusively diffuse plaques that are histologically similar to APs present in the brains of normal elderly individuals (Crystal et al., 1990) and AD patients. Pure LBD patients have few neuritic plaques (Dickson et al., 1989), which are typically found only in AD cases. Patients with common LBD have numerous diffuse plaques, but, as in pure LBD, may have fewer neuritic plaques than patients with AD (Dickson et al., 1989; Hansen et al., 1990; Lippa et al., 1994), although not all researchers agree on this point (Hansen et al., 1991).

In AD patients, APs develop first in polymodal association cortices of the frontal and temporal regions, and then accumulate in the hippocampus, amygdala, and remainder of the neocortex, with relative sparing of the primary motor and sensory cortices (Braak & Braak, 1991). To date, no study has systematically investigated the relative cerebral distributions of diffuse and neuritic APs in pure LBD or common LBD and compared these data to those from AD patients. Specific proteinaceous complex carbohydrates, or proteoglycans, found in APs differ between LBD and AD patients, but are identical in LBD and normal elderly individuals (Van Gool et al., 1993). This suggests that AP formation in LBD may be a pathological aging process that occurs concurrently with, but independently from, LBs *per se*. Early-onset cases (age 65 years or younger) of LBD typically have few or no APs (or NFTs; Kosaka, 1990), whereas most late-onset LBD patients (over age 65 years) have sufficient APs to satisfy current neuropathological criteria for a diagnosis of AD (Kosaka et al., 1984; Dickson et al., 1989; Hansen et al., 1990).

Another critical neuropathological difference between AD and LBD involves the distribution of NFTs. It is well known that most AD patients have a stereotypical distribution of NFTs that is initially most dense in the entorhinal cortex, and spreads to involve posterior temporoparietal and frontal association cortices, the hippocampus, and amygdala (Joachim et al., 1988; Braak & Braak, 1991). Some patients with the common form of LBD have a similar NFT distribution (Forno et al., 1978; Hansen et al., 1991). Several studies have now demonstrated, however, that overall NFT density in patients with common LBD is substantially lower than in patients with only AD pathology (Crystal et al., 1990; Hansen et al., 1990, 1991; Lippa et al., 1994), and the proportion of common LBD patients having NFTs generally appears to be lower than the proportion of AD patients having NFTs (Dickson et al., 1991). In patients with pure LBD, and in a significant subset of patients with common LBD, neocortical NFTs are virtually nonexistent (Hansen et al., 1993; Lippa et al., 1994; Hulette et al., 1995). Notably, NFTs are typically sparse or absent in the hippocampus, particularly in the CA1 region (Ikeda et al., 1980; Dickson et al., 1989; Crystal et al., 1990). This distribution contrasts with that of AD patients, where NFTs are typically numerous in the CA1 region of the hippocampus by the middle stages of the disease.

A particularly striking discrepancy between AD and LBD involves the hippocampal CA2–3 region. In AD, this zone is typically free of neuritic degeneration. In common LBD, Dickson et al. (1991) found that ubiquitin-immunoreactive neurites are present in the CA2–3 region, and they outnumber those found in the CA1 region. Cases with pure LBD had significantly more CA2–3 neurites than cases with common LBD. Furthermore, the immunoreactivity profile of CA2–3 neurites is similar to LBs, but is quite different from neurites found in AD. In addition, CA2–3 neuritic degeneration is strongly associated with the presence of cortical LBs in common LBD (Dickson et al., 1991; Kim et al., 1995). A final neuropathological distinction between AD and LBD involves a greater prevalence of spongiform encephalopathy restricted to the amygdala, entorhinal cortex, and superior temporal gyrus in LBD as compared to AD (Hansen et al., 1990).

Thus, the available evidence indicates some similarity, but several pronounced differences in the neuropathology of AD and LBD. Presumably, variations in the phenotypic expression of neuropathology (i.e., APs, NFTs, LBs) should be governed by one or more common, neuropathology-associated genotypes if LBD is to be considered a variant of AD. Conversely, the neuropathology-associated genotypes should be demonstrably different if LBD is independent of AD. Toward that end, the relative prevalence of various apolipoprotein E genotypes in patients with LBD, AD, and PD has been investigated recently.

Apolipoprotein E (ApoE)

The ϵ4 allele of the ApoE gene has been identified as a possible predisposing factor associated most closely with late-onset familial and sporadic AD. Individuals having the ϵ4 allele are at higher risk for the development of AD than those without it (Saunders et al., 1993). There may be a dose–response relationship between the ϵ4 allele and onset of AD, such that individuals having two ϵ4 alleles (type 4/4) may be at risk for earlier onset of AD than those with one ϵ4 allele (types 3/4 and 2/4), who, in turn, are at higher risk than individuals with no ϵ4 alleles (types 3/3 and 2/3; Corder et al., 1993). Marder et al. (1994) found that the frequency of ApoE ϵ2, ϵ3, and ϵ4 alleles was not different in PD patients with dementia compared to PD patients without dementia or normal elderly controls, suggesting that the cause of dementia in PD is independent of the ApoE gene product.

Several studies have now directly examined the relative frequency of the ApoE ϵ4 allele in AD and LBD. Galasko et al. (1994), Harrington et al. (1994), and St. Clair et al. (1994) found no differences in ϵ4 frequency between AD and common LBD patients, which supports the notion of common LBD as a variant of AD. Similarly, Gearing et al. (1995) found that the ϵ4 allele was equally overrepresented in patients with pure AD and those with concomitant AD and PD changes. However, when patients with pure LBD were examined, it was found that they had a significantly *lower* frequency of the ϵ4 allele (Galasko et al., 1994). Lippa

et al. (1995) obtained similar results; the ϵ4 allele frequency in common LBD patients did not differ from that found in LBD patients having mild to moderate AP deposition insufficient for a neuropathological diagnosis of AD, whereas pure LBD patients had a significantly lower frequency of the ϵ4 allele that was similar to that of age-matched nondemented subjects. Thus, the ApoE ϵ4 allele appears to be associated with the presence of cerebral APs but not LBs.

Comparative Clinical Characteristics

The first clinical description of patients with LBD suggested that emotional and behavioral symptoms were quite prominent, and frequently were the presenting feature (Woodard, 1962). Several subsequent case reports found that auditory and visual hallucinations, and delusions, were frequent presenting (Burkhardt et al., 1988; Kosaka, 1990) or early (Crystal et al., 1990) symptoms, with dementia and EPS developing later. Throughout the course of LBD and AD, the prevalence of psychopathology, including depression, hallucinations, delusions, impulsivity, agitation, and violent outbursts, may be higher in LBD than in AD. Direct comparisons of LBD and AD patients have found that acute and subacute confusional states (Perry et al., 1990), auditory and visual hallucinations, delusions (Dickson et al., 1987; McKeith et al., 1992, 1994), and depression (McKeith et al., 1992) were more common in LBD patients. These conclusions, however, are mitigated by a lack of neuropathological verification of LBD in some studies (McKeith et al., 1992; 1994), and by limited observations in others (Dickson et al., 1987; Perry et al., 1990).

Several other demographic and clinical features appear to distinguish AD from LBD patients. Although gender distribution in LBD has not been addressed in the literature, more men than women seem to be afflicted (see Table 3), which is similar to the distribution in PD (Mayeux et al., 1992). The age at onset of both pure and common LBD may be earlier than for AD; however, the data thus far are insufficient for direct comparisons between groups. The course of illness in LBD may be more rapid than in AD (Dickson et al., 1987; Byrne et al., 1989; Armstrong et al., 1991; Lippa et al., 1994), although it is unclear whether this is true both for pure and common LBD (Kosaka, 1990). EEG abnormalities in LBD consist of slowing of posterior background rhythms, as is often observed in AD. However, LBD patients may also show bursts of 2- to 4-Hz activity predominantly in the frontal regions (Crystal et al., 1990). Further, both types of EEG abnormality have been observed when LBD patients were only mildly demented, whereas the EEG abnormality in AD typically occurs later in the disease course (Kazniak et al., 1979).

The prevalence of EPS appears to be generally higher in LBD than in AD (Hansen et al., 1990; Perry et al., 1990). Interestingly, studies of EPS in AD largely preceded the widespread appreciation of LBD as a clinical entity. These studies have found that the prevalence of EPS in patients with a clinical diagnosis of AD ranges from 8% (Huff et al., 1987) to 100% (Sulkava, 1982), with modal estimates in the range of 20 to 40% (Sim & Sussman, 1962; Delwaide & Desseilles, 1977; Mölsä et al., 1984; Mayeux et al., 1985; Girling & Berrios, 1990). Prevalence rates probably vary as a function of a host of methodological differences across studies, and uncontrolled and confounding variables, including sampling bias (Sulkava, 1982; Tyrrell et al., 1990), greater dementia severity at study entry (Mölsä et al., 1984; Mayeux et al., 1985; Girling & Berrios, 1990; Förstl et al., 1992), the presence of vascular risk factors (Pearce, 1974), and current neuroleptic medication administration (Girling & Berrios, 1990), which tend to result in higher estimates of EPS. In addition, the specific type of EPS measured also varies between studies, and may serve to underestimate the overall prevalence of EPS in some AD samples (Huff et al., 1987; Förstl et al., 1992). Furthermore, few epidemiological studies of EPS in AD have been conducted. In a recent study of 236 patients with clinically diagnosed probable AD, 12% had at least one type of EPS judged not to have been induced by psychotropic medication (Stern et al., 1994).

Overall, studies suggest that the prevalence of EPS in AD is similar to the prevalence of neuropathologically confirmed LBD in patients having an antemortem clinical diagnosis of AD. Furthermore, rigidity and bradykinesia in clinically diagnosed AD patients were typically more frequent than was tremor (Pearce, 1974; Mölsä et al., 1984; Rinne et al., 1984; Mayeux et al., 1985), similar to the pattern of EPS observed in patients with LBD. Thus, it is possible that LBD may have accounted for a substantial proportion of cases of clinically diagnosed AD having EPS.

Cognitive deficits in LBD are similar in several respects to those seen in AD. In both AD and common LBD, memory disturbance is a central feature. The vast majority of patients with pure and common LBD demonstrate progressive dementia having an insidious onset. However, there have been rare exceptions in which no clinical dementia was detected in patients with neuropathologically confirmed LBD (Ikeda et al., 1978; Lippa et al., 1994). Several investigators have suggested that the pattern of cognitive impairments in LBD may be clinically distinguishable from AD and other forms of dementia. On a match-to-sample task involving delays of up to 12 s, LBD patients performed significantly worse than AD patients equated for age and level of global cognitive dysfunction (Sahgal et al., 1992). Shifting of attentional sets (Sahgal et al., 1992) and strategy formation (Sahgal et al., 1995) were found to be significantly poorer in LBD patients relative to age-matched AD patients, but spatial working memory was comparable. However, the findings of the latter three studies are significantly weakened by a lack of postmortem confirmation of the clinical diagnosis of LBD. In a cross-sectional study of cognitive impairment in LBD, Hansen et al. (1990) found that patients with neuropathologically confirmed common LBD showed disproportionate deficits in attention (WAIS–R Digit Span), visuospatial ability (WAIS–R Block Design, Copy-a-Cross Test), and verbal concept formation (WAIS–R Sim-

https://doi.org/10.1017/S1355617797001793 Published online by Cambridge University Press

Table 3. Clinical characteristics from case studies of patients with postmortem confirmed Lewy body neuropathology

Study	Age at onset (years)	Illness duration (years)	Sex (M:F)	Presenting symptoms D	E	D+E	NP	Psychopathology* H	Dl	Dp	A	F	N	Motor symptoms* B	R	T	G	M	N
Pure Lewy body disease																			
DeBruin et al., 1992	67	4	M		(gaze palsy)						+			+	+		+		
Gibb et al., 1985	27	3	F				+	+	+	+				+	+	+			
Ikeda et al., 1978	30	8	M		+								+	+	+		nr		
Kayano et al., 1980	38	12	M				+			nos				nr	+		nr	nr	
Mark et al., 1992	59	9	M	+				+						+	+		+		
Okazaki et al., 1961	68	1	M	+				+							+				
Sima et al., 1986[a]	66	6	M	1	1			0	0	0	1	0	2	2	1	0	1	0	1
Sugiyama et al., 1993	30	4	F		+					nos					+	+	nr	+	
Burkhardt et al., 1988	70.2 ± 4.1	4.1 ± 1.8	4:0	3	0	0	0	3	1	2	0	1	0	3	3	3	2	3	0
Byrne et al., 1989	71.4 ± 7.7	5.6 ± 4.9	6:5	3	5	3	0	2	1	3	0	10	7	9	10	7	10	0	1
Clark et al., 1986[b]	61.0 ± 16.1	10.7 ± 8.1	2:2	+								+	+		+	+	+		
Crystal et al., 1990[c]	74.7 ± 6.8	4.7 ± 0.6	1:2	+						+	+			1	3	2	3	0	0
Dickson et al., 1987[d]	67.5 ± 2.1	2.5 ± 0.7	(2)			nr		1	2	1	2	0	0	0	1	0	0	0	1
Förstl et al., 1993	65.5 ± 0.7	11.0 ± 2.8	2:0	1	1	0	0	1	1	0	0	0	0	0	2	1	1	1	2
Gibb et al., 1989	68.7 ± 2.6	4.0 ± 2.7	6:1	5	2	0	0	3	0	0	0	0	3	0	4	2	1	0	1
Kosaka, 1990[e]	32.8 ± 14.9	8.7 ± 3.5	6:3	0	7	0	2			(2 psychotic)				1	1	1	1	nr	0
Lippa et al., 1994[f]	71.6 ± 8.8	4.8 ± 3.6	3:2	3	0	0	1			+						3 nos			
Mixed Lewy body disease																			
Armstrong et al., 1991	65	1	F										+	+	+		+		
Burkhardt et al., 1988	75	1.5	M	+				+				+						+	
Delisle et al., 1987	36	13	M		(motor weakness)					nos						(increased tone)			
Forno et al., 1978	50	5	M	+						(agitation)					+	+	+	+	
Ikeda et al., 1980	69	3	M	+				(euphoria)			+	+							+
Kono et al., 1976	55	13	F		+					nr				+	+	+	nr		
Mark et al., 1992	73	13	F		+			+						+	+		+		
Tiller-Borcich & Forno, 1988	nr	nr	M			nr				+					+		+		
Yamamoto & Imai, 1988	64	4	M	+						nos					+		+		
Byrne et al., 1989	74.5 ± 5.9	5.2 ± 1.7	1:3	3	1	0	0	2	2	1	0	2	0	1	3	3	4	nr	0
Crystal et al., 1990	73.7 ± 5.9	7.7 ± 4.2	2:1			nr				nr				nr	3	0	3	nr	0
Dickson et al., 1987[d]	67.2 ± 7.6	4.8 ± 2.5	(4)			nr		2	1	0	2	0	1	0	3	2	1	0	0
Förstl et al., 1993	75.8 ± 4.4	5.2 ± 2.6	2:4	5	0	0	1	1	0	1	0	0	1	0	3	1	3	0	3
Gibb et al., 1985	53.0 ± 18.7	4.7 ± 1.4	2:1	2	0	0	1	2	1	0	0	1	1	2	3	3	1	0	0
Kosaka, 1990[e]	68.5 ± 10.1	5.7 ± 3.0	17:11	15	4	0	5			(5 psychotic)				nr	3	3	nr	nr	8
Kosaka, 1993[g]	61.4 ± 5.9	6.7 ± 4.5	8:3	9	2	0	0			nr				3	10	4	2	nr	0
Kuzuhara & Yoshimura, 1993	82.3 ± 7.4	6.5 ± 4.6	6:2	3	0	0	2	6	6	0	0	0	2	5	5	2	nr	0	3
					(3 dizziness)														
Lippa et al., 1994[f]	69.7 ± 12.8	6.2 ± 3.0	4:3	7	0	0	0			nr						3 nos			
Yoshimura, 1983	62.9 ± 4.5	5.1 ± 2.7	8:3			nr				nr				8	11	9	nr	0	0
Summary of clinical data for pure and mixed Lewy body disease																			
Pure LBD	60.4 ± 17.9	6.1 ± 4.2	37:19	43	37	6	10	36	17	24	14	35	12	46	76	43	58	19	15
Mixed LBD	67.2 ± 10.4	6.1 ± 3.5	54:34	64	12	0	12	47	37	7	10	10	33	48	77	40	70	1	18

A = aggression, B = bradykinesia, D = dementia, Dl = delusions, Dp = depression/irritability, E = EPS, F = Symptom fluctuation, G = gait disturbance, H = hallucinations, M = myoclonus, N = none, nos = present but unspecified, NP = neuropsychiatric symptoms, nr = not reported, R = rigidity, T = tremor, + = present, blank = absent. *Psychopathology and motor symptom categories not mutually exclusive. [a]Age at onset and illness duration were reported for one subject only, and presenting symptoms were reported for two subjects only. [b]Presenting symptoms, neuropsychiatric symptoms, and motor symptoms were reported for one subject only. [c]Presenting symptoms and neuropsychiatric symptoms were reported for one subject only. [d]Gender frequency was not reported. [e]Selected motor symptoms (B, R, T, M) reported for one subject only. [e]Summary data from review article, specific motor symptoms were reported for only one pure LBD and three common LBD patients. [f]One pure LBD patient had no cognitive, neurological, or psychiatric symptoms at death; neuropsychiatric symptoms were reported for one pure LBD patient only, and motor symptoms were reported for 3 pure and 3 common LBD patients only. [g]Specific motor symptoms were reported only in selected patients: bradykinesia ($n = 3$), rigidity ($n = 10$), tremor ($n = 10$), gait disturbance ($n = 2$).

ilarities) compared to age- and education-matched AD patients. In addition, while category fluency performance was comparable in LBD and AD patients, letter fluency (FAS) was significantly worse in the LBD patients. Within the heuristic framework defining cortical and subcortical dementias (Cummings & Benson, 1984), Hansen et al. (1990) interpreted this pattern of deficits as representing a combination of cortical and subcortical dysfunction.

Thus far, no study has comprehensively characterized the pattern of neuropsychological deficits associated with neuropathologically confirmed pure LBD, and how that pattern may differ from either common LBD or AD. Moreover, the influence of individual differences in LB distribution on the expression of specific cognitive deficits in any given patient has not been investigated. If the typical distribution of LBs in the cerebral cortex is associated with a specific pattern of cognitive deficits, those data would prove to be invaluable in the differential diagnosis of LBD from other dementia syndromes.

Fluctuations in the level of alertness, behavioral disturbance, and/or cognitive impairment that are not attributable to medications or intercurrent physical illness have been described frequently in LBD patients (Woodard, 1962; Forno et al., 1978; Ikeda et al., 1980; Clark et al., 1986; Gibb et al., 1985). In direct comparisons of clinically diagnosed LBD and AD patients, significantly more LBD patients than AD patients demonstrated fluctuating cognitive impairment (McKeith et al., 1992; 1994). In one series of histologically confirmed LBD, a fluctuating clinical course was noted in 80% of patients (Byrne et al., 1989). However, no systematic longitudinal investigations of cognitive and behavioral fluctuation in LBD have been reported. Furthermore, a fundamental problem in these reports is that the operational definition of what constitutes fluctuation of cognition and/or behavior has been vague. Finally, when symptom fluctuation has been examined, it is often unclear whether the fluctuation occurred in the cognitive or behavioral domain, or both.

META-ANALYSIS OF PURE AND COMMON LBD CASES REPORTED IN THE LITERATURE

Many of the clinical characteristics of LBD reported above are based on single or multiple case studies, not from group data. Therefore, firm conclusions about any differences between LBD, AD, and PD are elusive. However, informal comparisons of the clinical characteristics can be made using data amassed from the available case reports of LBD and contrasting these with data from numerous previous group-contrast studies of AD and PD. Toward this end, raw data for age at onset, illness duration, frequency of presenting symptoms, frequency and type of psychopathology, and the frequency and type of EPS were gathered from published case studies of patients with neuropathologically diagnosed LBD (see Table 3). In addition, formal analyses of clinical variables were performed using the raw data reported in those LBD case studies to determine if any reliable differences exist between the pure and common forms LBD.

Method

In order to perform this quantitative review of group differences between pure and common LBD, selection criteria for case studies were set, and clinical variables were defined as follows. First, to be included in the analysis, cases of LBD had to be neuropathologically confirmed. In some case studies, the presence of LBs was confirmed using only hematoxylin-eosin (H & E; Okazaki et al., 1961; Woodard, 1962; Forno et al., 1978; Ikeda et al., 1980; Yoshimura, 1983; Gibb et al., 1985, 1989; Burkhardt et al., 1988; Yamamoto & Imai, 1988), Bielschowsky silver (Clark et al., 1986), or other such basic histochemical staining methods. These methods are useful for the morphological identification of LBs, but are not specific to LBs. Many case studies employed immunocytochemical labeling methods, including antibody response to ubiquitin and/or tau proteins, in conjunction with basic stains. Although identification of LBs using only H & E and other basic stains may result in an increased risk of false positive LB identification, we decided to include those studies, but analyze them separately from studies employing immunocytochemical techniques.

Based on these staining methods, neuropathologically confirmed LBD cases were divided into those with pure LBD and those with common LBD. Common LBD cases were those that the authors of each case report defined as fulfilling minimal criteria for AD. For two reasons, individual cases of LBD could not be confirmed independently by us as meeting neuropathological criteria for concomitant AD. First, those criteria are semiquantitative (e.g., CERAD; Mirra et al., 1991) and so do not require specific counts of APs and NFTs. Second, there is variability in the methods and reporting conventions of individual investigators.

Using these selection criteria, 28 published reports on 150 cases of neuropathologically diagnosed LBD were selected and included in the analyses of clinical data. Of the 150 cases, 111 patients (48 pure; 63 common) had been reported in original case or group-design studies. The remaining 39 patients (10 pure; 29 common) were reported in reviews of the Japanese LBD literature (Kono et al., 1976, cited in Kosaka & Mehraein, 1979; Kayano et al., 1980, cited in Kosaka et al., 1984; Kosaka, 1990). Nine cases of pure AD and 25 cases of pure PD from studies comparing those patients directly with LBD patients were included in some analyses where possible.

A second set of analyses was performed, in which the grouping of cases was based upon descriptive neuropathology without the application of an inferential diagnostic status. The reasons for this grouping strategy are manifold. First, CERAD criteria for the neuropathological diagnosis of AD are arbitrary in that they are not based empirically on clinical correlates of pathological status. Second, most of the reports described unstandardized semiquantitative AD pa-

thology data. That is, the number of APs and NFTs are described with interpretive terms such as "rare," "sparse," "few," "infrequent," "mild," "moderate," and "severe." Third, because of the widespread use of unstandardized semiquantitative neuropathological assessment, most studies could not be evaluated as to whether any particular case unequivocally met neuropathological diagnostic criteria for AD. Fourth, criteria for AD have evolved, thus leading to some bias in the diagnosis of AD over time. For these reasons, we sought to avoid diagnostic labels and chose instead to apply a purely descriptive neuropathological approach.

Each patient was assigned to one of six groups according to the *presence or absence* of neuropathology: (1) LBs confined to the brainstem, (2) brainstem LBs and coexisting (but unspecified) AD pathology, (3) diffuse (brainstem and cortical) LBs only, (4) diffuse LBs with amyloid plaques only, (5) diffuse LBs with neurofibrillary tangles only, or (6) diffuse LBs, APs, and NFTs. Neither the severity of neuropathology nor whether pathology met published criteria for the neuropathological diagnosis of LBD or AD was taken into consideration.

Operational definitions

Ambiguities exist with some of the variables analyzed. Some clinicopathological case studies reported "age" rather than "age at onset" as a clinical variable. We believed it reasonable to assume that because these studies were primarily neuropathological, "age" represented age at death. Age at onset was then computed by subtracting the estimated duration of illness from the age at death. As noted above, the grading of LB, AP, and NFT densities in many studies was conducted using unstandardized, semiquantitative methods. Therefore, the diagnostic classifications of individual investigators were accepted for the purposes of the first set of analyses since definitive, objective assessment of those neuropathology counts was not possible. In cases where a range of neuropathological severity was reported, the maximum value was used for classification.

With respect to clinical variables, an explicit description of presenting symptoms was required for them to be coded as present or absent. Otherwise, presenting symptoms were treated as too ambiguous, and the data were coded as missing. Although we recognize that our selection of operational definitions (particularly for the variables "hallucinations," "delusions," and "depression") may result in systematic under- or overrepresentation, we argue that, given the current ambiguities, the operationalizations adopted herein draw a reasonable compromise between false-positive and false-negative errors.

Patients presenting with "disorientation," "forgetfulness," "difficulty dressing," or "memory impairment" were coded as presenting with *dementia*. Specific criteria for the presence of psychopathology were established because in some studies, they were clearly described, whereas in others, the descriptions were ambiguous. In most cases, it was unclear when any given emotional or behavioral symptom began if it was not a presenting symptom. Therefore, symptoms were coded only for presence or absence *at any time* during the patient's illness. *Hallucinations* and *delusions* had to be explicitly described as present; the descriptor "psychosis" was considered too nonspecific for coding in either of the latter two categories. *Depression* was coded when explicitly stated, or when mood was described as "depressed," "down," "low," or "irritable." *Aggression* was coded when explicitly stated, or when the patient's behavior was described as "assaultive," "violent," or as having engaged, or attempted to engage, in physically aggressive acts such as hitting or beating of others, or destroying objects.

Fluctuation presented a particularly difficult challenge for coding because of the ambiguity of the construct, potential for overlap with delirium or acute confusional states, and lack of consensus as to whether it should apply to the cognitive domain, behavioral domain, or both concurrently. For these analyses, a more stringent definition for fluctuation was adopted to minimize overinterpretation of clinical observations as being evidence of a "fluctuating" course. Specifically, *fluctuation* was coded as present when described explicitly or when salient variability in cognition, emotion, or behavior was reported in the case description. For example, fluctuation was coded when impairments were described as "intermittent," or when widely alternating levels of consciousness, emotional disturbance, or cognitive impairment were noted. The presence of "confusional states" was considered too nonspecific to be coded as evidence of fluctuation.

Results and Discussion

Researcher-defined groups

For the first set of analyses, pure and common LBD patients were grouped as defined by the authors of individual case studies. Using this method, a group of 58 pure LBD cases and a group of 92 common LBD cases were identified. The following set of analyses contrasts these two groups.

Age at onset was significantly younger in the pure LBD group [$t(143) = 2.91, p = .004$], but duration of illness was not significantly different between groups (see Table 4). Men outnumbered women in both the pure [$\chi^2(1) = 5.76, p = .02$], and common [$\chi^2(1) = 4.55, p = .03$], LBD groups by more than a 3:2 ratio. Gender distribution between pure and common LBD groups ($\chi^2 < 1$), however, was equivalent. These findings are consistent with the gender distribution in PD (Mayeux et al., 1992), but appear to differ from that in AD.

Patients with common LBD were more likely to present with dementia than were patients with pure LBD [$\chi^2(1) = 5.51, p = .02$], who in turn, were much more likely to present with EPS [$\chi^2(1) = 10.13, p = .001$; Table 3]. Within the patient groups, common LBD patients presented much more often with dementia (64%) than with EPS (12%) or psychopathology (12%) [$\chi^2(2) = 44.43, p < .001$], whereas pure LBD patients showed an equivalent likelihood ($\chi^2 < 1$) of

https://doi.org/10.1017/S1355617797001793 Published online by Cambridge University Press

Table 4. Mean age at onset and illness duration for patients with Lewy body pathology and varying Alzheimer's disease pathology for three sets of analyses

		Variable ($M \pm SD$)	
Group	N	Age at onset	Illness duration
Researcher-defined patient groups			
Pure LBD	54	60.4 ± 17.9	6.1 ± 4.2
Common LBD	91	67.2 ± 10.4	6.1 ± 3.5
Descriptive neuropathology groups, immunocytochemistry only			
dLB	11	39.1 ± 16.5	7.2 ± 3.6
dLB+NFT	8	48.4 ± 19.7	7.9 ± 3.6
bsLB	4	58.0 ± 7.9	6.2 ± 4.6
dLB+AP	8	64.0 ± 6.7	6.5 ± 4.4
dLB+AP+NFT	76	69.1 ± 9.7	6.2 ± 3.8
bsLB+AD	7	71.0 ± 8.1	5.6 ± 3.1

bsLB = brainstem Lewy bodies only, bsLB+AD = brainstem Lewy bodies and AD pathology, dLB = diffuse Lewy bodies only, dLB+AP = diffuse LB with amyloid plaques, dLB+NFT = diffuse Lewy bodies with neurofibrillary tangles, dLB+AP+NFT = diffuse Lewy bodies with amyloid plaques and neurofibrillary tangles.

presenting with either dementia (43%) or EPS (37%). There was no difference in the frequency with which the two patient groups presented with psychopathology ($\chi^2 < 1$), consistent with the observations of Kosaka (1990).

Over the course of their disease, the groups did not differ in terms of the prevalence of hallucinations or tendency toward aggressive behavior. However, delusions were marginally more frequent in common LBD patients [$\chi^2(1) = 3.42$, $p = .06$]. Pure LBD patients were more likely to show depressive symptoms [$\chi^2(1) = 3.76$, $p = .05$], and to have a fluctuating course [$\chi^2(1) = 5.76$, $p = .02$], than were common LBD patients. However, a single case report (Byrne et al., 1989) accounted for 10 of the 12 pure LBD patients described as having a fluctuating course, and thus may represent a diagnostic or definitional bias. Overall, the prevalence of any type of psychopathology was greater in pure LBD [$\chi^2(1) = 4.59$, $p = .03$].

The types of EPS did not differ between pure and common LBD patients. Common LBD patients were no more likely to demonstrate akinesia–rigidity-predominant EPS than were pure LBD patients ($\chi^2 < 1$). EPS limited to tremor (pure LBD: 12%; common LBD: 12%) was significantly less frequent than EPS limited to akinesia and/or rigidity (pure LBD: 37%; common LBD: 44%) in both the pure [$\chi^2(1) = 5.00$, $p = .03$], and common [$\chi^2(1) = 10.12$, $p = .002$] LBD groups. The frequency of gait disturbance did not differ between groups. However, substantial and equivalent proportions of pure LBD (30%) and common LBD (25%) patients demonstrated the classic PD motor triad of bradykinesia, rigidity, and tremor. Conversely, an equivalent proportion of pure (15%) and common (18%) LBD patients showed no EPS at any time during the course of their disease. Myoclonus was more frequent in pure LBD than in common LBD patients [$\chi^2(1) = 5.67$, $p = .02$].

Thus, the data suggest that the "typical" patient with a neuropathological diagnosis of pure LBD tends to be a man presenting early in his seventh decade with akinesia–rigidity-predominant EPS or with dementia. The dementia results in progressive deterioration of cognitive and social functioning, and is frequently accompanied by psychopathology, typically hallucinations or depression. Death usually occurs approximately 6 years following the onset of symptoms. The typical common LBD patient tends to be a man presenting in the middle to late portion of his seventh decade with dementia, followed by the onset of akinesia–rigidity-predominant EPS, with psychotic delusions being a frequent comorbid feature. Death also occurs about 6 years after symptom onset.

Descriptive neuropathology groups

For the second set of analyses, only case studies employing immunocytochemistry ($N = 114$) were selected in order to minimize false positive identification of LBs. The same analyses were conducted on all cases, including those with only basic histochemical staining methods. The results were essentially identical; therefore only the analyses for cases with immunocytochemistry are reported.

Patients were grouped according to a descriptive neuropathological status, yielding six groups: (1) 4 patients with LBs confined to the brainstem (bsLB), (2) 7 patients with brainstem LBs and coexisting (but unspecified) AD pathology (bsLB+AD), (3) 11 patients with only diffuse (brainstem and cortical) LBs (dLB), (4) 8 patients with diffuse LBs and amyloid plaques only (dLB+AP), (5) 8 patients with diffuse LBs and neurofibrillary tangles only (dLB+NFT), and (6) 76 patients with diffuse LBs, APs, and NFTs (dLB+AP+NFT). No attempt was made to determine if patients with concomitant AD pathology met either of two sets of accepted neuropathological criteria for AD (Khachaturian, 1985; Mirra et al., 1991).

Overall, age at onset was significantly different among the groups [$F(5,112) = 17.12$, $p < .001$; Table 4]. Illness onset in the bsLB, dLB, and dLB+NFT groups was not significantly different, but occurred at a significantly younger age than in the bsLB+AD, dLB+AP, and dLB+AP+NFT groups. No other differences in age at onset were significant. Illness duration was not significantly different across groups ($F < 1$). There were more men ($N = 9$) than women ($N = 2$) in the dLB group [$\chi^2(1) = 4.45$, $p = .03$]. However, analyses of gender distribution (and of clinical variables below) were limited by small groups sizes in all but the dLB+AP+NFT group. Interestingly, although the gender distribution in the dLB+AP+NFT group favored men ($N = 45$) over women ($N = 34$), the difference was not statistically significant [$\chi^2(1) = 1.53$, $p = .22$].

Analyses of clinical variables focused on the four groups with diffuse LB pathology and varying AD pathology: dLB, dLB+AP, dLB+NFT, and dLB+AP+NFT. LBD patients

https://doi.org/10.1017/S1355617797001793 Published online by Cambridge University Press

with or without limited AD pathology (APs or NFTs only) were more likely to present with EPS (85%) than with dementia [5%; $\chi^2(3) = 30.59$, $p < .001$], whereas patients with the combination of LBs, APs, and NFTs typically presented with dementia (58%) than with EPS [20%; $\chi^2(3) = 17.67$, $p < .001$]. There were no group differences in the frequency of hallucinations, delusions, depression, aggressive behavior, or fluctuation in course. However, the number of cases with adequate data reported for symptoms of psychopathology was quite limited ($N = 23$–26). The groups also did not differ in the frequency of bradykinesia, rigidity, tremor, gait disturbance, or myoclonus. Thus, these findings are consistent with those from the analysis of the researcher-defined groups in indicating an earlier age at onset, but similar illness duration, psychopathology, and motor symptoms for patients having LBs with no or limited AD pathology relative to patients with more extensive AD pathology.

To examine the effects of cortical LBs on clinical variables, above and beyond coexisting neuropathology, two final sets of analyses were performed. In the first analysis, patients with LBs limited to the brainstem (bsLB) were compared with patients with diffuse LBs (dLB). In the second analysis, patients having combined brainstem LBs and AD pathology (bsLB+AD) were compared to patients having diffuse LBs and the full complement of AD pathology (dLB+AP+NFT). Thus, in each of the two comparisons, the groups differed in terms of the presence or absence of *cortical* LBs, thereby estimating the effects that cortical LBs may specifically exert. The presence of cortical LBs was associated with an earlier age at onset in groups without concomitant AD pathology [bsLB: 58 ± 8 years *vs*. dLB: 39 ± 16 years; $F(1,14) = 4.69$, $p = .05$], but did not influence illness duration. The severity of dementia at time of death was greater in dLB than in bsLB groups (Mann-Whitney $U = 7.5$, $Z = -1.95$, $p = .05$). The presence of cortical LBs in the groups with concomitant AD pathology did not influence age at onset or illness duration. However, the severity of dementia was significantly greater in the dLB+AP+NFT group compared to the bsLB+AD group (Mann-Whitney $U = 168.5$, $Z = -2.58$, $p = .01$). Dementia was a more frequent presenting symptom in the dLB+AP+NFT group (62%) than in the bsLB+AD group (0%), whereas EPS was a more frequent presenting symptom in bsLB+AD patients (100%) than in dLB+AP+NFT patients [17%; $\chi^2(4) = 21.59$, $p < .001$]. Based on these analyses, the presence of cortical LBs appears to result in an earlier onset of illness and more severe dementia at the time of death.

Correlational analyses

The relationships between age at onset of LBD and the extent of LB and AD neuropathology were examined using Spearman nonparametric correlation coefficients. In patients with LBD, older age at onset was associated with greater amounts of AP in the cerebral cortex (Spearman's $\rho = .45$, $p < .001$), and greater amounts of NFT in the cerebral cortex ($\rho = .27$, $p = .005$) and hippocampus ($\rho = .46$, $p = .01$). These findings are consistent with Kosaka's (1990) assertion that LBD patients with an earlier onset (i.e., before age 65 years) have less AD pathology than do LBD patients with a later onset. In contrast, age at onset of LBD was not associated with greater amounts of cortical LBs ($\rho = .07$).

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

LBD is characterized by a distinct cerebral distribution of Lewy bodies and may or may not show the characteristic neuropathology of AD. LBD appears to be a more common cause of dementia than has been previously estimated. Based on available data, patients with diffuse LB pathology, with or without "limited" AD pathology (either amyloid plaques *or* neurofibrillary tangles, but not both), show an earlier age at onset than do patients with combined LBs, APs, and NFTs. In addition, they typically present with akinesia–rigidity-predominant EPS, and invariably develop dementia later in the course of their illness. In contrast, symptom onset in patients with the full complement of LBs, APs, and NFTs tends to be later, characterized by dementia, with EPS tending to occur after the onset of dementia. Furthermore, older age at onset of LBD is associated with greater amounts of AD pathology, but not with greater amounts of LB pathology. This suggests that, unlike AD pathology, the neuropathology of LBD is independent of age, and therefore may reflect a disease process that is independent of that in AD. In summary, LBD is neuropathologically distinct from both AD and PD, and there is evidence that it may be clinically distinct from both as well.

Most data from large-scale, prospective studies of LBD have been exclusively cross-sectional (e.g., Hansen et al., 1990; Förstl et al., 1993) and therefore do not provide the opportunity to investigate disease progression. Unfortunately, even the number of well designed group comparison studies of patients with LBD, AD, and PD is limited. Although some studies have examined limited longitudinal clinical data (Dickson et al., 1989; Crystal et al., 1990; Perry et al., 1990), no systematic, longitudinal study provides a comprehensive comparison of the nature and progression of cognitive impairments in LBD and AD patients. As a result, the correlation between neuropathology and progression of clinical symptoms has not been addressed.

The dementia syndrome of LBD consists of prominent memory impairment that may be accompanied by features of both cortical and subcortical dysfunction. However, because of methodological limitations in available studies, it is not known whether cortical LBs in numbers sufficient to meet proposed diagnostic criteria for LBD (Kosaka, 1990) consistently produce a distinct profile of cognitive dysfunction. The distinction between cognitive impairments caused by LBD and AD can be made only by comparing patients

https://doi.org/10.1017/S1355617797001793 Published online by Cambridge University Press

with pure LBD, those with pure AD, and those with concomitant AD and LBD pathology on a common set of clinical and cognitive measures over an extended time course. Attempts to describe the cognitive characteristics of patients with LBD without benefit of neuropathological confirmation appears to be an exercise in futility, as there are no data supporting the reliability or validity of the *clinical* diagnosis of LBD. Thus, we argue that in order to characterize the clinical (demographic, behavioral, cognitive, emotional) features of LBD accurately and differentiate them reliably from other dementing illnesses, longitudinal studies with neuropathological confirmation of LBD, using appropriate neuropathological techniques, are of critical importance.

The use of histological methods that are not sensitive or specific to LBs (Crystal et al., 1990; Sugiyama et al., 1994) may result in underestimating LB counts in patients who actually meet neuropathological criteria for LBD, failing to identify appropriate patients, or misidentifying similar neuropathological structures (e.g., globose NFTs) as LBs. Further, the regional distribution of respective pathologies must be determined. In our review of the literature, only 10 of 148 cases of pure and common LBD reporting demographic and clinical variables obtained specific counts of LB or AD pathology.

In addition to the wide variability in histological methods employed, procedures used for determining numbers of LBs, APs, and NFTs are largely unstandardized, semiquantitative, and subject to bias, thus making direct comparisons across cases and studies difficult. A reasonable solution involves reporting neuropathology counts in terms of density per square millimeter. This is equivalent to a 200× microscopic field of view. Cortical and subcortical areas to be examined should include, at minimum, three to four major LB predilection sites (substantia nigra, temporal cortex, insula, anterior cingulate gyrus, prefrontal cortex) and at least two control areas (e.g., occipital cortex), one of which should be the hippocampus. Finally, we propose that the term *mixed LBD–AD* be used for patients meeting neuropathological criteria for concomitant LBD and AD, rather than the term "common form" of LBD (Kosaka, 1990), because the relative prevalence of neuropathology in the population should have little bearing on disease nosology. Moreover, the proposed term is more purely descriptive, and therefore makes no assumption regarding pathological mechanisms.

Due to the limited number of well-designed group comparison studies, we suggest that several questions about the neuropathology and genetics of LBD require clarification. These issues include (1) the incidence of LB pathology in patients meeting criteria for the clinical diagnosis of possible or probable AD; (2) the distinguishing neuropathological characteristics of pure and mixed LBD, including the relative number and distribution of diffuse and neuritic plaques, and the proportion of all LBD patients having hippocampal and neocortical NFTs, and (3) the relative frequencies of ApoE genotypes in AD, PD, and both forms of LBD. In addition, several additional questions concerning the relationship of clinical indices among pure and mixed LBD, AD, and PD have yet to be investigated adequately. These include (1) demographic variables, including age at onset, presenting symptoms, duration of illness; (2) the frequency of behavioral and emotional disorders, including depression, psychosis, and fluctuation; (3) the frequency and type of EPS across illness duration; (4) the cross-sectional cognitive correlates of LB pathology, and (5) the comparable longitudinal clinical, cognitive, and behavioral characteristics of these diseases.

Because LBD has only recently been appreciated as an important clinical entity, it remains poorly understood. Basic questions concerning LBD should be addressed through the use of improved histological methods and research design. These methodological improvements will, in turn, provide a better understanding of LBD and its relationship to AD and PD.

ACKNOWLEDGMENTS

This project was funded in part by the John P. Boogher Fellowship in Memory Disorders (Dr. Cercy). The authors wish to thank Mark Becher, M.D., Jason Brandt, Ph.D., Claudia Kawas, M.D., and Pauline Maki, Ph.D., for helpful comments on an earlier version of this manuscript, as well as Lawrence Hansen, M.D., and an anonymous reviewer, for their insightful criticisms.

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