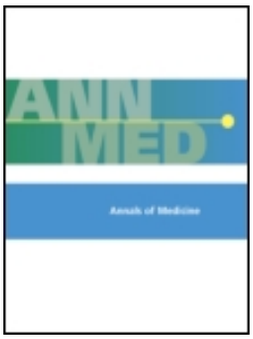

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◆ REVIEW ARTICLE ◆

Lewy body dementia

Daniel F Brown

Although Lewy body dementia (LBD) has received a considerable amount of interest in the last decade, there still exists a certain level of confusion concerning the clinical and neuropathological features associated with this disorder. According to many researchers, LBD represents a distinct dementing illness with specific clinical features. The neuropathological hallmark for this disorder is the Lewy body, a spherical intraneuronal cytoplasmic inclusion originally described in brainstem nuclei in Parkinson's disease. In LBD, Lewy bodies are found in subcortical nuclei, such as the substantia nigra, as well as diffusely in the neocortex. Recently, a consortium on dementia with Lewy bodies was held that established consensus guidelines for the clinical and pathological diagnosis of LBD. This review will focus on the newest developments in LBD, addressing specifically clinical and neuropathological features, diagnostic classification, genetics and potential pharmacotherapy.

Key words: Alzheimer's disease; dementia; Lewy body; Parkinson's disease.

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Introduction

In 1961, Okazaki and co-workers published the first description of diffuse Lewy bodies in the brains of two patients who presented with progressive dementia, parkinsonism and neuropsychiatric features. However, it is only in the last decade that this condition has received considerable interest. According to several published series (2–4), dementia associated with Lewy bodies now ranks second to only Alzheimer's disease (AD) as a cause of dementia. Vascular dementia, once considered the second most common cause of dementia, is now ranked third.

Despite the attention Lewy body dementia (LBD) has received in the literature, there still exists a considerable amount of confusion concerning both the clinical and neuropathological features associated with this entity. Much of the confusion centres around the nosology applied to cases in which dementia is present clinically and Lewy bodies are identified neuropathologically. Numerous terms have been used to describe the same or similar entities. Some of the more frequent terms encountered include diffuse Lewy body disease (5, 6) and senile dementia of the Lewy body type (3). The neuropathological hallmark for these disorders is the Lewy body, a spherical intraneuronal cytoplasmic inclusion originally described in brainstem nuclei in Parkinson's disease (PD) (5, 6). In LBD, Lewy bodies are found in subcortical nuclei, such as the substantia nigra, as well as diffusely in the neocortex (7–9). With the advent of more sensitive techniques to identify Lewy bodies, we now know that neocortical Lewy bodies are also commonly seen in idiopathic PD (10, 11), a finding that has created some controversy. Given the frequent clinical overlap in PD and LBD and the similar neuropathological features, some investigators feel that PD and LBD represent a phenotypic spectrum of the same disease process (8, 11).

Further adding to the confusion is the fact that concomitant neuropathological AD changes, ie senile plaques and neurofibrillary tangles, may also be present in LBD cases (2, 14–14). In fact, of those patients who present with dementia clinically and at autopsy meet the current criteria for a neuropatho-

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logical diagnosis of AD, as many as 30% will also have subcortical and neocortical Lewy bodies (2, 12–14). Hansen and co-workers coined the term the Lewy body variant of AD to describe such cases (2). Whether these cases truly represent a variant of AD or represent AD pathology superimposed upon LBD remains to be elucidated. As one can see, the true boundaries of LBD remain to be clearly defined given the significant clinical and pathological overlap with both AD and PD.

In an attempt to unify the terminology used for cases of dementia in which Lewy bodies are present, an international workshop (15) was held in October of 1995 that established consensus guidelines for the clinical and pathological diagnosis of 'dementia with Lewy bodies.' Although it was hoped that this consortium would eliminate some of the problems concerning diagnosis and classification of this disorder, there still seems to be some disagreement over what exactly these cases represent. This article will review the most recent developments in LBD addressing the clinical and neuropathological features most commonly associated with this disorder.

Clinical features

Demographics

According to a few studies, the prevalence of LBD does appear to be twice as high in males as in females (16, 17). The age of onset of LBD is similar to that for AD with a range of 50–85 years, depending upon the study (16, 18–20). Although most studies claim that the mean duration of illness tends to be shorter in LBD with a more rapidly progressive course than in age-matched AD patients, there is considerable variation. Durations of as short as 1 year and as long as 20 years have been reported, with the means generally falling between 3 and 6 years (16, 18, 19, 21).

Cognitive impairment

The cognitive impairment in LBD in many ways resembles the dementia of AD, although there do appear to be some key symptoms that are suggestive of LBD rather than AD (2, 3, 19, 22–25). As with AD, memory deficits are the initial complaint in about 70% of cases. However, LBD patients often experience fluctuations in their cognitive ability and performance (3, 19, 22). They also may have fluctuations in their alertness in the form of a confusional state or transient reduction in the level of consciousness (3, 19, 22). Loss of consciousness has also been reported (3, 19, 22). These fluctuations are important to recognize because they may be misinterpreted as vascular events or as sundowning. On neuropsychological testing, patients with LBD and AD exhibit similar deficits in memory and confrontation naming (26). However, studies have indicated that patients with LBD display disproportionally severe deficits in attention, fluency, visuospatial and constructional abilities, and psychomotor speed (2, 23). These features may help to distinguish LBD cases from typical AD cases.

Neurological findings

The clinical features of dementia and parkinsonism frequently coexist in LBD (3, 22). In fact, nearly 80% of LBD cases will develop extrapyramidal signs during the course of their illness (3), and in some cases spontaneous parkinsonism may precede intellectual decline (19, 27). From a diagnostic standpoint, these particular cases can be quite challenging as cognitive impairment is not uncommon in idiopathic PD (28–30). According to consensus criteria (15), a diagnosis of LBD is more likely if cognitive decline follows parkinsonism within the first year of the onset of the disease. It should be noted, however, that this 1-year interval is arbitrary and that it is frequently difficult to pinpoint the exact time of onset of cognitive decline or early extrapyramidal signs. The parkinsonian features in LBD tend to be milder and more symmetrical than in idiopathic PD (2, 18, 22). In addition, a resting tremor is uncommon, myoclonus may be more frequent, and response to levodopa is typically minor (31, 32). These features may be clinically helpful in distinguishing between these two disorders. There is also a special sensitivity to conventional neuroleptic drugs in LBD (33), with very low doses capable of inducing severe rigid–akinetic episodes even in patients who have not shown any previous symptoms. Finally, some researchers propose that unexplained falls are a prominent feature in LBD (22, 34). It is possible that the combination of impaired cognition including the transient loss of consciousness and the presence of extrapyramidal signs, such as rigidity, postural instability or even orthostatic hypotension, may predispose LBD patients to more frequent falls than other dementing illnesses or movement disorders.

Psychiatric features

Psychiatric symptoms in the form of depression, delusions and recurrent visual hallucinations are also a prominent feature of LBD (19, 20, 22, 35, 36). The hallucinations have been described as being persistent and complex, they tend to be well-formed and detailed, and they may last for days or even months. The hallucinations arise spontaneously and have no specific relation to medications. Recently, a study by Litvan and co-workers (37) demonstrated that hallucinations were in fact the best predictive diagnostic variable in the clinical diagnosis of LBD.

Clinical diagnostic criteria

As previously illustrated there do appear to be some clinical features that may be quite useful in distinguishing LBD from other dementing illnesses (2, 3, 19, 22–25). Since 1991, there have been three different sets of criteria established for the clinical diagnosis of LBD that have focused on these clinical features.

In 1991 the Nottingham Group for the Study of Neurodegenerative Diseases proposed one of the first structured criteria for the diagnosis of probable or possible LBD (38) (Table 1). There were some diagnostic problems with these criteria, however. As one can see, utilization of these criteria would allow for the inclusion of idiopathic PD cases (if A.2 were met) under the diagnosis of LBD. Furthermore, they would exclude those LBD cases in which there were no significant parkinsonian features.

In order to improve the diagnostic accuracy of LBD, McKeith and co-workers (22) proposed another set of criteria for the clinical diagnosis of LBD (Table 2) in 1992. These criteria were based upon the retrospective analysis of 21 autopsy-confirmed cases of LBD. With this method the most common misdiagnoses related to the failure to recognize the presence of fluctuations in the cognitive impairment of LBD patients.

More recently, a new set of criteria based largely on McKeith's original criteria were established during the 1995 Proceedings of the First International Workshop of the Consortium on Dementia with Lewy Bodies (15). The Report of the Consortium described consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (Table 3) and was published in 1996. These criteria were modified from McKeith's original criteria, specifically taking into account the difficulty in recognizing fluctuations in cognitive impairment.

Table 1. Proposed clinical diagnostic criteria for probable and possible dementia associated with cortical Lewy bodies (reproduced from (38) with permission).

I. Diagnostic criteria for *probable* dementia associated with cortical Lewy bodies

A. At least one of the following
1. Gradual onset of dementia syndrome (that fulfills the *Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised, ie* DSM-III-R, criteria) with prominent attentional deficits or the appearance of apparent acute confusional states early in the course, for which no underlying toxic metabolic infective or other cause is identified. DSM-III-R criteria for dementia include demonstrable evidence of memory impairment and either impairment in one other intellectual function (abstract theory, judgement and higher cortical functions such as aphasia, apraxia and agnosia) or a personality change.
2. 'Classical' Parkinson's disease (defined as levodopa-responsive parkinsonism) at onset with the latter emergence of dementia syndrome (as described in 1 above)
3. Simultaneous occurrence at onset of dementia (as described in 1 above) and parkinsonism

B. Both of the following
1. Absence of any unequivocal history of stroke
2. No focal signs other than parkinsonism

C. At least three of the following symptoms, which may be mild and occur late in the disease progression
1. Tremor
2. Rigidity
3. Postural change
4. Bradykinesia
5. Gait abnormality

D. Other causes of dementia or parkinsonism have been excluded

II. Diagnostic criteria for *possible* dementia associated with cortical Lewy bodies

A. At least one of the following
1. Dementia (as described in 1 above) with acute onset and rapid course, sometimes associated with plateau and frequently associated with psychiatric symptoms (depression or delusional states)
2. Dementia (as described in 1 above) with late presentation of parkinsonian symptoms that fulfill criterion B below

B. One or two of the following
1. Tremor
2. Rigidity
3. Postural change
4. Bradykinesia
5. Gait abnormality

C. Both of the following
1. Absence of any unequivocal history of stroke
2. No focal signs other than parkinsonism

D. Other causes of dementia or parkinsonism have been excluded

Neuropathology

Neuropathological features

The pathological hallmark of idiopathic LBD is the presence of intraneuronal inclusions called Lewy bodies. Frederich H Lewy first described these inclusions in the substantia innominata and the dorsal motor nucleus of the vagus in 1912 (5). They were termed 'corps de Lewy' or Lewy bodies by Tretiakoff 7 years later when he linked the clinical signs and symptoms of parkinsonism with degeneration of the substantia nigra in patients suffering from PD (6). The first cases of diffuse Lewy bodies were described by Okazaki in 1961, who identified widespread Lewy bodies in the substantia nigra, locus coeruleus and diffusely in the neocortex in two demented elderly individuals (1). Following Okazaki's report, several other investigators reported similar cases of widespread Lewy bodies in the brains of patients dying with a predominantly dementing illness (9, 39–41).

Lewy bodies are concentric, spherical, eosinophilic, cytoplasmic inclusion bodies found within neurones. Lewy bodies have been identified in surviving neurones

Table 2. Proposed operational criteria for senile dementia of Lewy body type (reproduced from (22) with permission).

A. Fluctuating cognitive impairment affecting both memory and higher cortical functions (such as language, visuospatial ability, praxis or reasoning skills). The fluctuation is marked with the occurrence of both episodic confusion and lucid intervals, as in delirium, and is evident either on repeated tests of cognitive function or by variable performance in daily living skills.

B. At least one of the following
1. Visual and/or auditory hallucinations which are usually accompanied by secondary paranoid delusions
2. Mild spontaneous extrapyramidal features or neuroleptic sensitivity syndrome, ie exaggerated adverse responses to standard doses of neuroleptic medication
3. Repeated unexplained falls and/or transient clouding or loss of consciousness

C. Despite the fluctuating pattern the clinical features persist over a long period of time (weeks or months) unlike delirium which rarely persists as long.

D. Exclusion of any underlying physical illness adequate to account for the fluctuating cognitive state, by appropriate examination and investigation.

E. Exclusion of past history of confirmed stroke and/or evidence of cerebral ischaemic damage on structural brain imaging.

Table 3. Consensus criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB) (reproduced from (15) with permission).

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal–subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of probable DLB, and one is essential for a diagnosis of possible DLB
   - **a.** Fluctuating cognition with pronounced variations in attention and alertness
   - **b.** Recurrent visual hallucinations that are typically well formed and detailed
   - **c.** Spontaneous motor features of parkinsonism
3. Features supportive of the diagnosis are
   - **a.** Repeated falls
   - **b.** Syncope
   - **c.** Transient loss of consciousness
   - **d.** Neuroleptic sensitivity
   - **e.** Systematized delusions
   - **f.** Hallucinations in other modalities
4. A diagnosis of DLB is less likely in the presence of
   - **a.** Stroke disease, evident as focal neurologic signs or on brain imaging
   - **b.** Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

in numerous subcortical nuclei, including the substantia nigra, locus coeruleus, dorsal motor nucleus of the vagus, thalamus, hypothalamus and the amygdala (42). They can also be found in limbic and neocortical neurones (43). Lewy bodies have slight morphological differences depending upon where they are located. Brainstem Lewy bodies have a dense hyaline core with a surrounding pale halo and are easy to identify in routine haematoxylin and eosin (H&E)-stained sections (Fig 1). Cortical Lewy bodies tend to be slightly smaller, less round, and lack the dense core and well-developed halo of brainstem Lewy bodies. They can be difficult to identify in H&E-stained sections. Immunohistochemistry has aided in the ability to identify more readily neocortical Lewy bodies as they are immunoreactive for ubiquitin (44) and α-synuclein (45, 46) (Fig 2).

Ultrastructurally, Lewy bodies are composed of filamentous, vesicular and granular structures. The major components of Lewy bodies are neurofilament proteins (47–50), structural proteins (47) and synaptic proteins (45, 46, 51, 52). Lewy bodies also contain

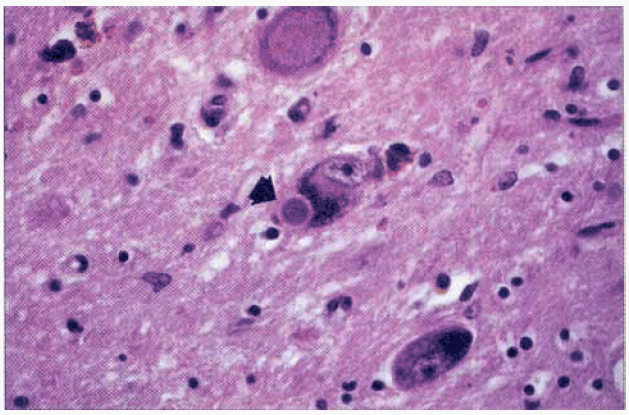

Figure 1. Photomicrograph of a Lewy body (arrow) within the cytoplasm of a substantia nigra neurone (haematoxylin and eosin staining, 125x).

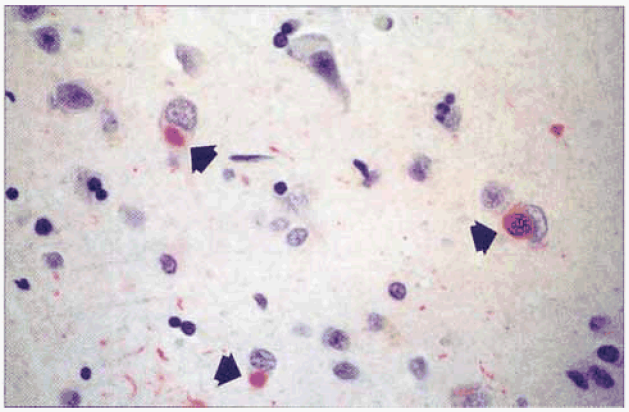

Figure 2. Photomicrograph of intraneuronal neocortical Lewy bodies (arrows) highlighted with immunohistochemistry for α-synuclein. Lewy neurites can also be seen in the background (red chromogen, 63x).

ubiquitin (53, 54), a protein that 'tags' abnormal proteins for nonlysosomal degradation.

Additional pathology associated with the Lewy body disorders includes the presence of Lewy neurites as first described by Dickson and co-workers (55). Lewy neurites are dystrophic processes, axons or dendrites, that also contain neurofilament proteins and α-synuclein. They resemble the dystrophic neurites commonly seen in AD brains, yet they lack the microtubule-associated protein tau. Lewy neurites are found in the CA2–3 region of the hippocampus, in the amygdala, in brainstem nuclei, and diffusely throughout the neocortex.

It is well established that AD pathology is also often found in association with Lewy body pathology (2, 12–14). Significant numbers of senile plaques are found in the majority of LBD cases, and these are morphologically indistinguishable from those found in pure AD (56). In many cases, these plaques are not tau immunoreactive, and in 80–90% of LBD cases there is no evidence of significant tau pathology, including neocortical neurofibrillary tangles (57). However, there is a certain percentage of cases in which plaques, neocortical tangles, and diffuse Lewy bodies all coexist. The presence of diffuse Lewy bodies does not exclude a diagnosis of concomitant AD. The clinical diagnosis in such cases might be quite challenging if extrapyramidal signs or visual hallucinations are not part of the clinical picture.

The distinction from PD may also be somewhat difficult. In fact, cases of PD and LBD may be neuropathologically indistinguishable as both can have subcortical and neocortical Lewy bodies (8). A recent study showed that in 100 cases of idiopathic PD neocortical Lewy bodies were present in all cases (10).

The similarities in the clinical phenotypes and neuropathology of LBD with both AD and PD has led some investigators to propose that LBD does not exist as a distinct clinicopathological entity (11). Rather, some feel that it represents mixed AD and PD (58, 59). Future investigations into the molecular genetics underlying these disorders will ultimately clarify this issue.

Classification

Many investigators feel that Lewy body formation proceeds in an organized neuroanatomical pattern, progressing from a brainstem pattern to a limbic pattern to a neocortical pattern. Kosaka was one of the first investigators to recognize this hierarchy and divided LBD into 'brainstem', 'transitional', and 'neocortical' categories (8). These categories were adapted and included in the consensus criteria for the pathological diagnosis of dementia with Lewy bodies, and are based upon Lewy body frequency in specific brain regions (15).

Clinicopathological correlations

There is considerable debate in the literature as to the morphological substrate of the cognitive impairment in LBD. It is well recognized that the loss of synapses (60–62), severity of neocortical neuropil threads (63), and density of neocortical tangles (64–66) all correlate with severity of dementia in typical AD. The density of senile plaques, however, does not (64, 65). In LBD the substrate is probably multifactorial with contributions from AD pathology, neocortical Lewy bodies (67), and ultimately neocortical synapse loss (68, 69). In those cases without concomitant AD pathology there are conflicting studies as to correlations between dementia and neocortical Lewy body frequency (3, 70). It is possible that the loss of subcortical input to the neocortex (2, 3) may contribute to the cognitive impairment seen clinically, similar to what has been described for PD (71). For example, it is known that the cholinergic input to the neocortex from the nucleus basalis of Meynert is severely affected in LBD (71, 72).

The parkinsonism that frequently accompanies the cognitive impairment in LBD may be explained by Lewy body formation in the substantia nigra as is the case with idiopathic PD (6). However, not all cases of LBD develop extrapyramidal signs (15). It is more likely that the severity of neuronal loss rather than the presence of Lewy bodies in surviving neurones results in the clinical movement disorder. The substantia nigra can compensate until about 70–80% of the nigrostriatal dopamine neurones are lost (73). It is possible that in those cases without extrapyramidal signs, although Lewy bodies are present, the threshold for clinical symptomatology may not have been exceeded.

Genetics

An area of recent excitement involving PD was the identification by Polymeropolous and co-workers (74) of a single gene mutation in four unrelated Mediterranean families with autosomal dominant PD. A second mutation in this gene was subsequently identified in another kindred (75). The gene is located on chromosome 4q21–23 and encodes a presynaptic nerve terminal protein called α-synuclein. α-synuclein was later found to be one of the major components of Lewy bodies and Lewy neurites (45, 46, 52). Although genetic factors have been implicated in some cases of LBD involving several pedigrees with an autosomal dominant inheritance pattern (76, 77), the α-synuclein mutations have not been found in cases of LBD (78), in other PD families (79–82), or in sporadic PD cases (78, 83, 84). This suggests that PD and LBD are genetically heterogeneous. Furthermore, α-synuclein accumulations do not appear to be specific for the

Lewy body disorders as they have been identified in the glial cytoplasmic inclusions of multiple system atrophy (85), a heterogeneous neurodegenerative movement disorder. Interestingly, a truncated fragment of the α-synuclein protein was originally identified as the non-Aβ component (NAC) of the senile plaques in AD (86–88) and may represent a link between LBD and AD.

Pharmacotherapy

Patients with LBD have a greater cholinergic deficit than patients with typical AD (71, 72, 89). Some studies have shown a comparably stronger or qualitatively different response to the acetylcholinesterase inhibitors tacrine and donepezil in LBD patients (90–92). Although the parkinsonian features seen in LBD may respond to levodopa, the response is generally mild and certainly not as strong as for patients with idiopathic PD (31, 32).

One key feature of LBD is the associated unusual hypersensitivity to neuroleptics (33). Treatment of behaviour disturbances and psychotic episodes with common antipsychotic medications, such as haloperidol and phenothiazines, has been associated with severe and sometimes irreversible side-effects. However, there are some antipsychotic drugs available that some researchers agree can be used to treat psychosis and mood symptoms in LBD effectively. Agents in this category include risperidone (93), clozapine (94) and odansetron (95). It should be advised, however, that even with these atypical neuroleptics and new antipsychotic drugs some patients may be intolerant of these medications, and can develop worsening confusion and behavioural symptoms (96–98).

Conclusion

The relationship between LBD, PD, and AD is complex and incompletely understood. There are many who feel that LBD is a distinct clinical and neuropathological entity with specific enough symptomatology and neuropathological features to warrant its diagnosis. However, there certainly are dissenters to this opinion who claim that both the clinical and neuropathological features represent a combination of PD and AD in the same patient. They argue that LBD represents a spectrum of varying clinical phenotypes depending upon the relative neuropathological involvement of AD and PD changes. A better understanding of the pathogenesis of LBD and its relationship to AD and to PD will likely require an accumulation of clinical, neuropathological, and genetic information. However, given the potential therapeutic implications including decreased responsiveness to levodopa and the tendency toward severe neuroleptic sensitivity, most researchers recommend utilizing the consensus guidelines for the clinical diagnosis of dementia with Lewy bodies in suspected cases.

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