Cortical Lewy body disease

D J Burn

Cortical Lewy body disease reflects the presence of cortical Lewy bodies but without a clear clinical correlation

Cortical Lewy body disease is a pathological observation rather than a distinct clinicopathological entity. Cortical Lewy bodies (CLB) are typically found in Parkinson’s disease and dementia with Lewy bodies (DLB), although they may also occur in other neurological disorders. Unlike their brain stem counterparts, CLB are less distinctive and are poorly visualised using conventional histochemical methods. The protein α-synuclein is the main component of Lewy bodies and the related dystrophic Lewy neurites; immunohistochemistry using antibodies raised against this protein has greater sensitivity in demonstrating Lewy pathology within the cerebral cortex than histochemical methods and anti-ubiquitin immunohistochemistry.

Dementia is a common occurrence in Parkinson’s disease, with a prevalence of 20–40% in cross sectional studies, but a cumulative incidence approaching 80%. The clinical phenotype of this dementia shares many features with DLB. In neither condition, however, has the relation between the presence of CLB and the dementing process been clearly defined. The situation is complex in that there are several possible pathophysiological mechanisms that may underpin cognitive impairment in both Parkinson’s disease and DLB (table 1).

This therefore leads to various fundamental questions regarding the role of the CLB and the contribution of this inclusion to dementia in DLB and Parkinson’s disease. Given the heterogeneous processes involved, the degree of interaction or synergism occurring between α-synuclein pathology and, for example, Alzheimer-type pathology that results in dementia also needs to be established.

RELATION BETWEEN DLB AND PARKINSON’S DISEASE

Clinically, Parkinson’s disease with dementia (PDD) and DLB share many phenotypic similarities. Familial forms of Parkinson’s disease and DLB have been described. Cognitive impairment in both conditions has significant executive and visuospatial-visuoconstructual components, often with relatively preserved mnemonic function early in the disease course. Visual hallucinations are a core diagnostic feature for DLB (table 2) and are also common in PDD. Parkinsonism may not always be present in DLB cases, particularly at disease onset, but appears in the majority as the condition progresses. Consensus criteria artificially divide patients with parkinsonism and dementia according to a “one year rule”: cases with a history of parkinsonism of less than one year are classified as DLB, whereas those who develop dementia after more than 12 months of Parkinson’s disease are designated PDD.

Pathologically, three types of DLB are recognised—brain stem predominant, limbic (transitional), and neocortical. CLB density cannot, however, separate cases of DLB from PDD. In common with DLB, the cognitive and neuropsychiatric problems in PDD appear to respond to cholinesterase inhibitors without worsening of the extrapyramidal features, although the outcome of ongoing double blind, placebo controlled trials is needed to confirm this.

FORMATION AND CONSTITUTION OF LEWY BODIES

In DLB, Lewy pathology in the cerebral cortex affects layers V–VI initially, then layer III, and finally layer II. Topographically, the amygdala is first affected, then the insula and limbic cortex, and finally the neocortex. Chronic axonal transport blockage is implicated in the development of CLB. Intraneuronal Lewy pathology begins in the axonal terminal, before involving the cell body and finally the dendrite. α-Synuclein first accumulates in neuronal cytoplasm without filamentous components. Lewy bodies and Lewy related neurites then form, composed of granulo-filamentous components, before the inclusions are degraded to extracellular Lewy bodies; the processes of tumour necrosis factor α and inducible nitric oxide synthase positive astrogia are in close association. As well as α-synuclein, amyloid precursor protein, chromogranin-A, synphilin-1, and synaptophysin accumulate in CLB from an early stage in their evolution. Torsin A—a protein with homology to yeast heat shock protein 104—also colocalises with α-synuclein in Lewy bodies. Double immunostaining of Lewy bodies using antibodies to α-synuclein and a panel of monoclonal antibodies to phosphorylated and non-phosphorylated tau epitopes spanning the length of the tau molecule reveals tau immunoreactive Lewy bodies in the medulla of 80% of cases of Parkinson’s disease and DLB. Interestingly, tau tends to coaggregate with α-synuclein in neurones most vulnerable to NFT formation—for example, the locus coeruleus and the basal nucleus of Meynert.

There is a close relation between aggresomes—cytoplasmic inclusions formed as a cytoprotective response to sequester and degrade potentially toxic abnormal proteins—and Lewy bodies. Lewy bodies sequester the ubiquitin activating enzyme, E1, and the E3 ubiquitin ligase, parkin, which are also recruited to aggresomes for enhanced proteolysis. Inhibition of proteasomal function or generation of misfolded proteins causes the formation of aggresome/Lewy body-like inclusions and cytotoxicity in dopaminergic neurones in culture.

EVIDENCE AGAINST CLB AS THE SOLE CAUSE OF DEMENTIA

The case for CLB playing an exclusive role in the genesis of dementia in PDD and DLB is weakened by several lines of evidence. For example, all Parkinson’s disease brains, from demented cases or not, may have CLB. Additionally, some workers have found no correlation between regional CLB density and any clinical symptoms of DLB, while the neuropathology of non-demented patients with Parkinson’s disease may be indistinguishable from that of patients with brain stem and limbic DLB. In a recent study, 17 cases of Parkinson’s disease were reported where no history of cognitive impairment was ever recorded in life, yet pathologically these cases—which were typical of Parkinson’s disease—also fulfilled diagnostic criteria for either limbic or neocortical types of DLB.

Others have linked PDD more closely with Alzheimer-type pathology. Moderate to severe dementia was reported in 33% of 200 consecutive cases

Abbreviations: CERAD, consortium to establish a registry for Alzheimer’s disease; CLB, cortical Lewy bodies; DLB, dementia with Lewy bodies; NFT, neurofibrillary tangle; NIA, National Institute on Aging; PDD, Parkinson’s disease with dementia

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of Parkinson’s disease at necropsy in one series. The degree of cognitive impairment was significantly correlated with Alzheimer’s disease pathology, using CERAD (consortium to establish a registry for Alzheimer’s disease), Braak, and NIA–Reagan criteria (see table 3 for an outline of CERAD and NIA–Reagan diagnostic criteria), while the degree of Alzheimer’s disease pathology was negatively correlated with survival. Alzheimer lesions corresponding to CERAD B or C were seen in 84% of the demented patients with Parkinson’s disease. Regional neurofibrillary tangle (NFT) counts have been correlated with dementia in Parkinson’s disease. Thus in one small series of cases, although there were no significant group differences in allocortical or neocortical Lewy body counts between demented and non-demented groups, mean entorhinal NFT severity ratings were more than twice those for non-demented cases. Senile plaque densities were also greater in every cortical region measured for demented versus non-demented cases of Parkinson’s disease. Furthermore, the degree of “Alzheimerisation” by tangle pathology reduces the clinical diagnostic accuracy for DLB (39% for pathologically confirmed DLB cases with high Braak stages, compared with 75% for cases with low Braak stages). DLB patients with a higher NFT burden are also less likely to have visual hallucinations than those with low NFT density. Vascular amyloid β deposition is more common in brains from elderly (demented and non-demented) patients with Parkinson’s disease than in age matched controls. Cognitive impairment in Parkinson’s disease is, however, largely independent of coexistent vascular pathology, except in cases with severe cerebrovascular disease.

### Table 1 Possible pathophysiological mechanisms for dementia in Parkinson’s disease and dementia with Lewy bodies

<table>
<thead>
<tr>
<th>Anatomical substrate</th>
<th>Subcortical</th>
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<tbody>
<tr>
<td></td>
<td>Loss of ascending projections from pigmented brain stem nuclei</td>
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<td></td>
<td>Prefrontal-caudate nucleus “disconnection”</td>
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<td></td>
<td>Intrinsic cortical pathology</td>
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<tr>
<td>Neurochemical substrate</td>
<td>Cholinergic deficiency</td>
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<td></td>
<td>Dopaminergic hyperfunction</td>
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<td></td>
<td>Other monoaminergic neurotransmitter deficiencies</td>
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<tr>
<td>Neupathological substrate</td>
<td>Lewy bodies and dystrophic neurites</td>
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<td></td>
<td>Alzheimer-like changes (plaques and neurofibrillary tangles)</td>
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<td></td>
<td>Vascular pathology</td>
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</tbody>
</table>

### Table 2 Consensus criteria for clinical diagnosis of probable and possible dementia with Lewy bodies

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social and 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 and visuospatial skills may also be especially prominent.

2. Two of the following core features are essential for a diagnosis of probable DLB and one is essential for possible DLB:
   - Fluctuation of cognition with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous motor features of parkinsonism

3. Features supportive of the diagnosis are:
   - Repeated falls
   - Syncope
   - Transient loss of consciousness
   - Neuroleptic sensitivity
   - Systematised delusions
   - Hallucinations in other modalities
   - REM sleep behaviour disorder
   - Depression

4. A diagnosis of DLB is less likely in the presence of:
   - Stroke disease, evident as focal neurological signs or on brain imaging
   - Evidence of physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

*Not described in original criteria but subsequently proposed to assist with diagnosis.

DBL, dementia with Lewy bodies.

### EVIDENCE FOR CLB AS A PRIMARY CAUSE OF DEMENTIA

In contrast with the above, other series have found that CLB density—especially in the temporal neocortex—correlates significantly with cognitive impairment in Parkinson’s disease, independent of or in addition to Alzheimer type pathology. Furthermore, a detailed clinico-pathological study recently showed that high Lewy body densities in the amygdala and parahippocampus correlated well with formal visual hallucinations. Parahippocampal Lewy body density may differentiate PDD from DLB and non-demented Parkinson’s disease cases with over 90% accuracy, and is reported to be a better pathological marker for dementia than neuritic plaques. CLB—demonstrated using α-synuclein immunohistochemistry—have also been reported by others to be both highly sensitive (91%) and specific (90%) neuropathological markers for PDD, and better indicators of dementia than NFT, senile plaques, or dystrophic neuritis. Nevertheless, 10% of patients in this series with neuropathological changes typical of Parkinson’s disease and judged during life to be demented had no cortical pathology of note (that is, no CLB, nFT, or senile plaques).

Apaydin and colleagues have recently reported that mean and median Lewy body counts were increased nearly 10-fold in the neocortex, limbic cortex, and amygdala in demented compared with non-demented cases of Parkinson’s disease. Patients with high CLB counts in one region were likely to have high counts in other areas. Although Alzheimer type pathology was described as “modest” in this series, there were significant correlations between CLB counts and senile plaque and (to a lesser extent) NFT counts.

### RECONCILING THE DIFFERENCES: SYNERGISM NOT POLARISATION

How does one reconcile the apparently divergent views on the role of CLB in causing dementia in Parkinson’s disease and DLB? There are various methodological reasons that may go some way to account for the disparity. Thus several clinicopathological studies reported correlations before the advent of more sensitive α-synuclein immunohistochemical techniques, and may therefore have underestimated CLB and Lewy neurite densities. Also, the pathological diagnostic criteria widely used for Alzheimer’s disease now place greater emphasis upon the presence of NFT, rather than the older Khachaturian criteria used in some previous studies, where senile plaque density was regarded as more important.
Notwithstanding these methodological issues, most studies have commented upon coexisting pathology in the cerebral cortex of PDD and DLB cases, with CLB and a variable admixture of Alzheimer like pathology. Furthermore, several investigators have commented upon significant correlations between CLB counts and senile plaque density in particular, while cases of pure DLB with no senile plaques or NFT are uncommon. 34 Recent observations also suggest that processes involved in the misfolding and formation of CLB and abnormalities in the accumulation of β amyloid protein (Aβ) and metabolism of tau protein may not be entirely independent. Regarding Aβ, doubly transgenic mice expressing the human form of this protein, as well as α-synuclein, develop severe memory and learning deficits in addition to motor problems. 35 Doubly transgenic mice also develop more α-synuclein immunoreactive inclusions than α-synuclein singly transgenic mice. Furthermore, Aβ peptides can promote aggregation of α-synuclein in cell-free systems and intraneuronal accumulation of α-synuclein in cell culture. Tau, associated with NFT, is a microtubule associated protein involved in intra-axonal microtubular assembly and stabilisation. Tau immunostaining is often present at the periphery of Lewy bodies, 36 and it has been suggested that interaction between tau and α-synuclein may facilitate protein aggregation. 37 The tau H1 haplotype has been associated with clinically diagnosed Parkinson’s disease, 37 although a recent study of 157 pathologically confirmed cases did not find any significant relation to tau haplotype status. 38 However, the latter study did not differentiate between demented and non-demented cases. It is thus still possible that an association with tau haplotype may predominate to PDD, rather than Parkinson’s disease in general.

An interaction between α-synuclein and Alzheimer type pathology also has potential implications for patient management and treatment approaches. Recent work has shown that patients with Parkinson’s disease exposed to long term (more than two years) anti-cholinergic drug treatment have 2.5-fold higher cortical densities of senile plaques than patients with short term or no exposure to these drugs. 39 In the same study, NFT densities were also increased in the chronically treated group. Although preliminary, these data raise the possibility that anticholinergic drugs—currently commonly used to treat bladder dysfunction—or tricyclic antidepressants with anticholinergic properties may actually induce a pathological substrate for dementia in Parkinson’s disease. Conversely, cholinergic agonists can reduce cerebrospinal fluid Aβ concentration in patients with Alzheimer’s disease 40 and cortical Aβ levels in animal models. 41 Such agents may therefore be worth exploring for disease modifying benefits in patients with Parkinson’s disease with early cognitive impairment.

CONCLUSIONS

Cortical Lewy body disease reflects the presence of CLB but without a clear clinical correlate. Although CLB may be found in various neurological disorders they are most commonly associated with Parkinson’s disease and DLB. The dementia syndrome that is central to the diagnosis of DLB and a frequent occurrence in Parkinson’s disease has been variably linked with CLB topography and density. The common co-occurrence of α-synuclein and Alzheimer type pathology, however, suggests that a combination of pathologies related to protein dysmetabolism, possibly with a synergistic protein–protein interaction, is the most probable explanation underpinning the cognitive impairment in these disorders, and that dementia will ensue when a “toxic threshold” is reached, irrespective of the combination of pathologies involved in reaching that threshold. Future studies should elucidate further the nature of the putative protein–protein interaction, identify whether there are specific clinical correlates of these pathological processes, find robust biomarkers to reflect the relative contribution of Lewy related and Alzheimer type pathology to the dementia, and explore the rational use of drugs that can reduce α-synuclein aggregation and β amyloid production.

Table 3 Summary of CERAD 26 and NIA–Reagan Institute pathological criteria for Alzheimer’s disease 27

<table>
<thead>
<tr>
<th>Categories</th>
<th>CERAD criteria</th>
<th>NIA–Reagan Institute criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Semiquantitative assessment of neuritic plaque density, graded by “cartoon” comparison as sparse, moderate, and frequent</td>
<td>All lesions considered (amyloid deposits, neuritic plaques, neurofibrillary tangles and NFT)</td>
</tr>
<tr>
<td>Sampling of multiple cortical areas and midbrain</td>
<td>“Age-related plaque score” and topographic staging of NFT combined with clinical information</td>
<td></td>
</tr>
<tr>
<td>Generation of “age related plaque score”</td>
<td>Probabilistic approach for diagnosis of dementia</td>
<td></td>
</tr>
<tr>
<td>Categories</td>
<td>0 No evidence of Alzheimer’s disease</td>
<td>Low probability: CERAD “sparse” and Braak stage I/II</td>
</tr>
<tr>
<td></td>
<td>A Uncertain evidence of Alzheimer’s disease</td>
<td>Intermediate probability: CERAD “moderate” and Braak stage III/IV</td>
</tr>
<tr>
<td></td>
<td>B Suggestive of Alzheimer’s disease</td>
<td>High probability: CERAD “frequent” and Braak stage V/VI</td>
</tr>
<tr>
<td></td>
<td>C Indicative of Alzheimer’s disease</td>
<td>Very high probability: CERAD “very frequent” and Braak stage VI/ VII</td>
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</tbody>
</table>

CERAD, consortium to establish a registry of Alzheimer’s disease; NFT, neurofibrillary tangle; NIA, National Institute on Aging.

REFERENCES

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