Clinicopathological Correlates of Lewy Body Disease: Fundamental Issues

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Lewy body pathology (LBP) is the pathological hallmark of Lewy body diseases, such as Parkinson’s disease and Lewy body dementia. Recent studies have shed new light on the role of LBP, the interactions of LBP with concomitant pathologies, and the propagation of LBP from the olfactory bulb and enteric nervous system to the central nervous system. The intrinsic difficulty with identifying clinicopathological correlates could be overcome by improving our understanding of the pathological evolution of LBP.

Key Words: Lewy body, Lewy body disease, Parkinson’s disease, Lewy body dementia.

The Formation of Lewy Body

On hematoxylin-eosin staining, many LBs in the brainstem consist of an eosinophilic core and peripheral halo, whereas they usually appear as irregular eosinophilic inclusions in other limbic and cortical areas. Of the numerous proteins contained in LBs, α-synuclein (αSyn) is the most abundant, and many of the proteins are ubiquitinated. The central predominance of αSyn and the peripheral halo of densely ubiquitinated proteins is a conspicuous feature of brainstem LB.

The organized feature of brainstem LBs implies order in the process of LB formation. The aggresome hypothesis holds that the failure of the aggresome to remove unwanted proteins is a primordial event. A LB might form from a failed aggresome, but not in a haphazard way. Consequently, LB formation could be an ‘active’ process designed to segregate harmful proteins from the neurons.

The pathogenesis of PD has been discussed in association with cellular machinery such as the proteasome and autophagy for the removal of unwanted proteins. Direct evidence of this came from human brain, which showed structural defects in, and functional impairment of, the proteasome. Experimental studies recapitulated neuronal death and the formation of αSyn aggregates by proteasomal inhibition, which could be considered as a forme fruste of LB. Autophagy is another important system for dealing with toxic waste. Interestingly, chaperone-mediated autophagy was hampered by a mutant αSyn or αSyn-dopa adducts, forming αSyn aggregates. These data suggest that the formation of the LB is closely related to the impairment of major intracellular machinery. However, the ultimate upstream mechanism responsible for the active regulation of the machinery that handles toxic waste by segregating it into...
aggregates is still under investigation.

The Role of the Lewy Body

The neuroprotection conferred by LB formation has been studied in the human brain using in-situ end-labeling for apoptosis, in which the neurons with LBs were less frequently apoptotic than those without.\(^17\) Another study showed the downregulation of tyrosine hydroxylase (TH) in the neurons harboring LBs.\(^18\) The presence of LBs might alert the neurons to prepare for the threat to come. As TH is a key enzyme in the metabolism of dopamine in the SN, and dopamine oxidation can produce highly toxic products, such as dopamine adducts, TH downregulation could be an effective compensatory way to survive.

As LB is commonly found in a background of severe neuronal loss, as in the case of PD, LB cannot be easily exempted from neuron death. A recent pathological study showed a stable proportion of LB-containing neurons in the SN, suggesting a balance between the formation and removal of LBs.\(^19\) The authors calculated the lifespan of neurons with LB to be 6.2 months versus 15.9 months for those with any type of aSyn inclusion. The limited life span of the neurons carrying LBs argues for the detrimental role of LBs.

Without prospective data, it cannot be determined whether LB formation signifies a tombstone for a cell death cascade or a successful salvage operation to sequester toxicants. However, recent studies have partly suggested that the LB is not necessarily a culprit in neuronal death.

Incidental Lewy Body Disease

Incidental Lewy body disease (iLBD) is a pathological entity defined by the presence of aSyn pathology without any clinical evidence of PD or DLB. As iLBD is found in normal persons, by definition, its pathology offers invaluable insight into the early evolution of LBD, such as PD and DLB.\(^20,22\) Moreover, although iLBD has no clinical implications, by definition, it is significantly associated with a clinical prodrome of PD that includes olfactory dysfunction and bowel frequency, which provide a pathological basis for the early diagnosis of PD.\(^23,24\)

In iLBD, the neuronal loss is usually minimal, despite aSyn pathology.\(^20,22\) The dissociation between neuronal loss and aSyn pathology contrasts the marked neuronal death and widespread LBP in the SN in PD, which suggests that LBP is less toxic than expected, at least in iLBD. Then, if iLBD is a true prodrome of PD and its pathology recapitulates the early evolution of the LBP of PD, the transition from iLBD to PD may be made by additional provoking factors, rather than by a simple shift in the continuum of LBD.

When microgliosis and astrogliosis are studied in the brainstem nuclei, including the dorsal motor nucleus of the vagus nerve (dmV) in the medulla, locus ceruleus (LC) in the pons, and SN in the midbrain, neuroinflammation is only increased slightly in iLBD, compared to normal controls, whereas inflammatory change is conspicuous in PD.\(^25\) Interestingly, although the inflammatory change was similar in the three brainstem nuclei in iLBD, the SN was more severely affected by neuroinflammation than the dmV and LC in PD. The drastic change in inflammation might underlie the pattern shift of LBP from iLBD to PD. Other potential factors contributing to the pattern shift are a high iron content, excessive oxidative stress, and impaired anti-oxidative mechanism.\(^26,28\) The disproportionate involvement of the SN is in line with the conspicuous motor manifestations of PD, closely associated with SN pathology, while no clinical symptoms are present in iLBD.

The recent hypothesis on the caudo-rostral propagation of LBP suggested by Braak assumes that the appearance of aSyn pathology in SN is a key feature of entering the symptomatic phase.\(^29,30\) However, there are many iLBD cases with an extra-nigral distribution, even involving the neocortices.\(^23\) In fact, some cases with iLBD could be classified as a DLB-like group, due to the widespread distribution of aSyn pathology. iLBD could be ‘pro-PD’ (brainstem predominant iLBD) or ‘pro-DLB’ (diffuse iLBD).\(^22\) These findings suggest the occurrence of LBP across the brain without a significant temporal gap, not respecting the border between the brainstem and cortices, rather than in a consecutive manner from the lower brainstem to the higher cortices, without skipping intervening tissues.

Concomitant Pathologies

Another difficult problem is that iLBD is not exclusively related to LBD. Other neurodegenerative diseases can accompany LB, such as Alzheimer’s disease (AD) and progressive supranuclear palsy.\(^31,32\) A small proportion of the patients with multiple system atrophy and corticobasal degeneration also have associated LBD.\(^33\) As LBP is found in normal subjects and patients with various neurodegenerative diseases, it is possible to say that LBD might develop in any brain, regardless of the concomitant pathologies.\(^31\) This again raises a vexing question about the functional contribution of LBP.

To understand the functional role of LBP, it is necessary to have at least two sets of data: one concerning the quantitative relationship between the clinical features and the burden of LBP, and the other concerning the interaction with other concomitant pathologies, to isolate the ‘pure’ contribution of LBP. Surprisingly, although cognitive function was reported to be correlated with cortical LBs, few studies have succeeded in showing a significant relationship between Parkinsonism and aSyn pathology. A recent prospective study showed that Parkinsonism was significantly correlated with the burden of aSyn pathology.\(^34\)

Facing the problem of mixed AD and LB pathology in DLB,
researchers adopted the concept of probability to discriminate the functional significance of the specific pathologies. The cases heavily loaded with AD pathology are less likely to be diagnosed as DLB, even with diffuse LBD according to the published consensus criteria. Recently, Obi et al. studied β-amyloid, tau protein, and LBP together and showed the central role of β-amyloid in the evolution of tau pathology. LBP was not entirely dependent on β-amyloid pathology. These attempts underscore the importance of sifting through concomitant pathologies to identify the independent contribution of LBP.

Apart from AD pathologies such as tau [neurofibrillary tangle (NFT)] and β-amyloid [senile plaque (SP)], other pathologies might modify the clinicopathological presentation of LBP; these include, vascular pathologies, argyrophilic grain disease (AGD) and TAR DNA binding protein-43 (TDP43). AGD and TDP43 could contribute to cognitive decline, which would be difficult to discern in the context of coexisting limbic AD pathologies or cortical LBs. Vascular pathologies have a more complicated implication because they show great variability in terms of the amount and distribution of the lesions. A comprehensive approach that considers all of the coexisting pathologies together is needed to determine a full picture of the clinicopathological interactions, and to delineate the role of LBP.

**Propagation of Lewy Body Pathology**

Recent studies of fetal grafts demonstrated the propagation of the aSyn pathology from the host to the graft, which unraveled the contagious nature of aSyn pathology. Until recently, only grafts more than 10 years after transplantation were thought to be insinuated by aSyn pathologies, and earlier studies showed no aSyn pathologies in grafts younger than 10 years.

Several mechanisms were suggested to explain the human pathology. In a recent case, a graft was studied 14 years after transplantation. Although the graft was expected to be localized in the putamen, it had extended from the putamen to the amygdala. aSyn inclusions were found in the graft, and they were more frequent in the portion lying in the amygdala. Astrogliosis and microgliosis were also more prominent in the amygdala portion of the graft. The myelination of the graft was poor and mainly found in the putaminal portion. Corpora amylacea (as a marker of aging) was more common in the peripheral portion of the graft. These findings indicated that the maturation and aging of the graft might not be critical to the development of aSyn pathology. As the amygdala is more severely affected than the putamen in LBD, and could frequently be affected by various abnormal protein aggregations, such as NFTs, TDP-43, and argyrophilic grains, the amygdala might have a greater tendency to develop pathological inclusions than the putamen. In other words, the putamen-amygdala gradient of aSyn inclusions might be affected by factors constituting the ‘aggregation-prone’ milieu of the amygdala, which remains speculative. Recently, cell-to-cell propagation of aSyn inclusions was demonstrated experimentally. As the pathologic burden of aSyn was heavier in the amygdala, the propagation might explain the putamen-amygdala gradient. Direct propagation from the neighboring tissue might produce a center-peripheral gradient of aSyn inclusions in the graft, which was, however, not observed in our case.

**Conclusions**

After its birth in iLBD, LBP might ‘mature’, affecting various regions with or without concomitant pathologies. It remains controversial whether LBP spreads from limited pathological foci (the enteric nervous system or olfactory bulb according to the hypothesis of Braak) or arises nearly simultaneously, but disproportionately, in multiple sites. In some cases of AD, only the amygdala is affected by LBP, sparing other brain areas involved in the classical forms of LBD, which argues for the latter scenario. Recent data showed that the explanatory power of Braak staging for LBP is variable, and is most compelling in LBD associated with progressive supranuclear palsy. As LBP commonly accompanies other pathologies, its functional role should be dissected from the influence of concomitant pathologies.

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