"Untangling" the relationship between Alzheimer disease and dementia with Lewy bodies

Russell H. Swerdlow, MD
Kathy L. Newell, MD

Correspondence & reprint requests to Dr. Swerdlow: rswerdlow@kumc.edu

Neurology® 2012;79:1938–1939

Lewy bodies, protein aggregations classically associated with Parkinson disease (PD) substantia nigra neurons, are not limited to the brainstem.[1] Over time, pathologists developed terms such as "diffuse Lewy body disease" (DLBD) to describe autopsy cases in which Lewy bodies even extended to the neocortex.[2] Efforts soon followed to define a clinical syndrome that predicted histopathology-defined entities such as DLBD.[3] Eventually, formal international consensus criteria that emphasized dementia with varying combinations of parkinsonism, visual hallucinations, and cognitive/level of consciousness fluctuations were proposed.[4] Clinicians embraced the new disease entity these criteria defined, dementia with Lewy bodies (DLB), applying it mostly to patients with concomitantly evolving dementia and parkinsonism. Not surprisingly, even though parkinsonism is not a requisite feature, neurologists have largely come to think of DLB as an Alzheimer disease (AD) and PD overlap syndrome.

AD and DLB histologic features also overlap. Brains of patients who have been clinically diagnosed with DLB often have, in addition to brainstem and cortical Lewy bodies, neurofibrillary tangles and (especially) β-amyloid plaques. Pervasive clinical and histologic overlap necessarily raises the question of whether DLB truly constitutes an independent disorder,[5] and if not, does it more likely represent an AD or PD variant?

In this issue of *Neurology*®, Tsuang et al.[6] present a study that informs this debate. The authors considered brain pathology data from 562 individuals who experienced dementia during life and 267 individuals who had not. Before death, subjects had been followed at AD centers, and no one carried a clinical PD diagnosis. Brains were categorized according to the presence or absence of substantial Lewy body and AD pathology. The 267 autopsied control brains showed at most limited Lewy body or AD pathology. Also included as controls were an additional 124 living subjects without dementia presumed to lack significant Lewy body or AD-associated protein aggregations. The *GBA* gene that codes for glucocerebrosidase, causing Gaucher disease when both copies are mutated,[7] and that increases PD risk when one copy is mutated,[8] was sequenced in 562 subjects with dementia and 391 control subjects.

Within the dementia group, 14% were considered "pure" DLB (pDLB) cases that had Lewy body but not AD pathology, 41% had Lewy body disease (LBD) extending beyond the brainstem and AD pathology (LBD-AD group), and 45% had AD but not Lewy body pathology. Twenty-five *GBA* mutations were found within the 953 sequenced subjects. These mutations were not distributed equally among the groups. The pDLB group had the highest *GBA* mutation frequency, both the AD and control groups had low *GBA* mutation frequencies, and the LBD + AD group had an intermediate *GBA* mutation frequency. These data reveal that in addition to increasing PD risk, heterozygous *GBA* mutations also increase DLB risk. The authors reasonably conclude, therefore, that at a molecular-pathology level, DLB is more closely related to PD than it is to AD.

This conclusion is further supported by the fact that sex distributions differed between the groups. As is the case with most PD but not AD cohorts, the pDLB group was predominantly male.[9] Also, because study subjects derived from AD centers, and PD-diagnosed patients were not included, the pDLB group was probably not contaminated by PD that had simply progressed to a PD dementia syndrome.

Study limitations include the fact that subjects considered to have DLB in this study were not diagnosed with DLB during life. The authors state this is because most subjects died before current DLB consensus criteria were published.[10] Thus, whereas subjects with pDLB and LBD + AD by definition certainly had LBD and usually DLBD, it is unclear whether individuals in these groups had clinically di-

See page 1944

From the University of Kansas Alzheimer's Disease Center, Kansas University Medical Center, Kansas City.
Study funding: R.H.S. is supported by P30 AG035982 and NS 077852. K.L.N. is supported by P30 AG035982.
Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this editorial.

agnosable DLB syndromes. Although relationships between ethnicity and *GBA* mutation frequencies are recognized, ethnic distributions were not ascertained. Because the number of *GBA* mutations was low to begin with, and these mutations were further diluted among several groups, chance could have affected the outcome. Finally, although this study confirms an association between *GBA* mutation and synucleinopathy, it provides little insight into why individuals with dementia frequently show mixed Lewy body and AD pathologies. In mixed pathology cases, therefore, the neuropathologist cannot truly provide an absolute diagnosis, but instead predicts the "likelihood" that AD or DLB was the responsible entity.[10]

Although debate over whether DLB constitutes a unique disease entity will continue, for now, the Tsuang et al. study pushes the DLB pendulum toward PD and away from AD. A conceptual inference is that in the future, disease-modifying agents developed to treat PD might predictably benefit patients with DLB more than disease-modifying agents developed for AD. A practical implication is that when it comes to neuroleptic sensitivity profiling, it is worth considering that patients with DLB without prominent parkinsonism may have the same biological predisposition to adverse side effects as patients with DLB with prominent parkinsonism.

DISCLOSURE

Dr. Swerdlow receives grant support from NIH and serves on the editorial board of *Neurology*. Dr. Newell receives grant support from NIH. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Shults CW. Lewy bodies. Proc Natl Acad Sci USA 2006; 103:1661–1668.
2. Byrne EJ, Lennox G, Lowe J, Godwin-Austen RB. Diffuse Lewy body disease: clinical features in 15 cases. J Neurol Neurosurg Psychiatry 1989;52:709–717.
3. Crystal HA, Dickson DW, Lizardi JE, Davies P, Wolfson LI. Antemortem diagnosis of diffuse Lewy body disease. Neurology 1990;40:1523–1528.
4. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124.
5. Benecke R. Diffuse Lewy body disease: a clinical syndrome or a disease entity? J Neurol 2003;250(suppl 1):I39–I42.
6. Tsuang D, Leverenz JB, Lopez OL, et al. *GBA* mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. Neurology 2012;79:1944–1950.
7. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat 2008;29:567–583.
8. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651–1661.
9. Tanner CM, Goldman SM. Epidemiology of Parkinson's disease. Neurol Clin 1996;14:317–335.
10. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.