Neurodegeneration in Parkinson disease

Moving Lewy bodies out of focus

Walter J. Schulz-Schaeffer, MD, PhD

Correspondence & reprint requests to Dr. Schulz-Schaeffer: wjschulz@med.uni-goettingen.de

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The neuropathologic diagnosis of Parkinson disease (PD) is based on the detection of Lewy bodies in the substantia nigra of patients with a Parkinson syndrome, although the connection between Lewy bodies and the neurodegenerative process is still unclear. Furthermore, the presence of Lewy pathology is not an indicator of clinical PD, regardless of the brain area in which it is found. Lewy bodies can be found at autopsy, age-dependently, and in patient numbers that exceed the prevalence of PD by one order of magnitude.[1] It is under debate whether these incidental asymptomatic persons with Lewy bodies (ILB) have preclinical PD.[2]

Attempts to correlate the number of Lewy bodies, which are composed mainly but not exclusively of α-synuclein, with clinical measures such as the duration of PD, have failed (for review, see reference[3]). The percentage of substantia nigra neurons that contain these insoluble protein aggregates seem to be relatively stable over time.[4] No correlation has been found between Lewy body content in the substantia nigra and decrease of dopamine transporter in the putamen, or nigral neuronal loss, although a decrease of dopamine transporter and neuronal loss correlate with the total α-synuclein burden.[5] Moreover, it might be that Lewy body–containing neurons are perhaps the more viable ones. There is some evidence that Lewy body formation is an aggresome-related process that segregates excess amounts of unwanted, possibly cytotoxic, proteins.[6] Given the fact that only a small percentage of the α-synuclein aggregates in Lewy body–related diseases is deposited in the form of complex Lewy aggregates (Lewy bodies or Lewy neurites)[7] and α-synuclein is physiologically located at axon terminals, the Lewy body formation may reflect a detoxification process. This would support the notion that Lewy pathology is an indirect measure of the neurodegenerative process in PD.

In this issue of *Neurology*®, Milber et al.[8] report on the dysfunction of neuromelanin-containing substantia nigra neurons, based on tyrosine hydroxylase immunoreactivity; and on degeneration, based on neuron densities in PD, incidental Lewy body–presenting persons and controls, in comparison to Lewy pathology and the Braak PD stages. The patients were from the longitudinal prospective Honolulu-Asia Aging Study of risk factors for developing PD or dementia. Comparing the 33 ILB and 13 PD subjects, ILB with Braak stage 5/6 had a significantly lower Lewy pathology burden, as assessed by semiquantitation using a score of 0 (none) to 4 (severe), than PD with Braak stage 5/6; however, there was no significant difference in the mean age at death. The neuron density in ILB was intermediate between the controls (n = 17) and the patients with PD, but the percentage of tyrosine hydroxylase–negative substantia nigra neurons was higher in ILB than in PD and controls. Nigral neuron density decreased with the severity of Lewy pathology burden, but nigral tyrosine hydroxylase negativity did not show a correlation with the amount of Lewy pathology. When comparing ILB of different Braak stages, the mean neuron density and neuronal dysfunction levels were relatively constant.

These results are highly relevant because the authors show for the first time that neuronal dysfunction and cell loss may precede the Lewy pathology. Before Lewy pathology was detectable by conventional immunohistochemical methods, neuronal dysfunction and cell loss could be observed in the substantia nigra in ILB at a level that does not differ in the mean from those of higher Braak stages. This report may help to change the view on Lewy pathology. From the clinical perspective, it is evident that PD is caused by a synaptic failure. In vivo imaging studies of synaptic functions of the CNS found compelling evidence for presynaptic neurotransmitter deficiencies in PD. These findings, together with the fact that dopamine-replacement therapy, the breakthrough of the last century in managing PD, is so effective, leaves little doubt that the degenerative process must be located at the presynapse.[9]

If α-synuclein aggregates do have a role in PD, PD dementia, and dementia with Lewy bodies, they must be located at synapses or must be involved indirectly in the synaptic failure. Indeed, recent studies demonstrated the presynaptic accumulation of α-synuclein aggregates in dementia with Lewy bodies[7] and PD[9] and showed that the amount of α-synuclein aggregates located at synapses in the form of small aggregates exceeded the classic Lewy pathology by 1 to 2 orders of magnitude.[7] Postsynaptic dendritic spines retract, most likely as an effect of the presynaptic pathology.[7] α-Synuclein aggregation might

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From the Prion and Dementia Research Unit, Department of Neuropathology, University Medical Center Göttingen, Germany.

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be directly or indirectly involved in axon degeneration. The amount of neurons with axon degeneration exceeds the nigral neuron loss at the time of PD diagnosis by 100%.[10] Intra-axonal α-synuclein accumulation occurs as part of Lewy pathology and may impair axonal transport functions. Several reports suggest that the neurodegenerative process starts at axonal terminals and proceeds in a retrograde direction (reviewed in references[3] and [10]).

The results reported by Milber et al.[8] are yet another piece in the growing body of evidence pointing us toward the need to rethink our current concepts of neurodegeneration and disease progression. We should disengage from the notion of Lewy body–associated cell death as the main phenomenon in PD and concentrate on synaptic pathology and axonal degeneration of still-existing cells in our search for therapy and for understanding the pathophysiology of PD.

DISCLOSURE

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REFERENCES

1. Markesbery WR, Jicha GA, Liu H, Schmitt FA. Lewy body pathology in normal elderly subjects. J Neuropathol Exp Neurol 2009;68:816–822.
2. Dickson DW, Fujishiro H, DelleDonne A, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta Neuropathol 2008;115:437–444.
3. Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 2012;27:8–30.
4. Greffard S, Verny M, Bonnet AM, et al. A stable proportion of Lewy body bearing neurons in the substantia nigra suggests a model in which the Lewy body causes neuronal death. Neurobiol Aging 2010;31:99–103.
5. Kovacs GG, Milenkovic IJ, Preusser M, Budka H. Nigral burden of alpha-synuclein correlates with striatal dopamine deficit. Mov Disord 2008;23:1608–1612.
6. Olanow CW, Perl DP, DeMartino GN, McNaught KS. Lewy-body formation is an aggresome-related process: a hypothesis. Lancet Neurol 2004;3:496–503.
7. Kramer ML, Schulz-Schaeffer WJ. Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies. J Neurosci 2007;27:1405–1410.
8. Milber JM, Noorigian JV, Morley JF, et al. Lewy pathology is not the first sign of degeneration in vulnerable neurons in Parkinson disease. Neurology 2012;79:2307–2314.
9. Schulz-Schaeffer WJ. The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. Acta Neuropathol 2010;120:131–143.
10. Cheng HC, Ulane CM, Burke RE. Clinical progression in Parkinson disease and the neurobiology of axons. Ann Neurol 2010;67:715–725.