

The pathological substrate of visual hallucinations in Parkinson's disease patients.

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Research questions and background

Visual hallucinations (VH) and cognitive impairment are frequent and important clinical symptoms in Lewy Body diseases, including Parkinson's disease (PD), Parkinson's disease dementia (PDD), and Dementia with Lewy Bodies (DLB). A cholinergic deficit and concomitant Alzheimer's disease (AD) pathology, especially Amyloid- β (A β) aggregates, are suggested to contribute to these symptoms. To investigate these issues we set out two research questions:

1. Is there neuronal loss and concomitant AD pathology in the pedunculopontine nucleus (i.e. the major cholinergic center in the brainstem; PPN) of PD and DLB patients with visual hallucinations?
2. Are there differences in distribution and load of A β pathology in PD, PDD and DLB patients?

Methods and tissues used

To address the first research question we used postmortem brainstem tissue samples of 9 clinically diagnosed and pathologically confirmed PD patients with VH, 9 DLB patients with VH, and 9 age- and sex-matched nondemented controls, that were obtained from the Netherlands Brain Bank. Using a morphometric approach, we estimated the density of cholinergic neurons in the compact part of the PPN (PPNc) and determined the local load of α -synuclein-immunoreactive Lewy pathology, neurofibrillary tangles and A β plaques.

To answer the second research question, we identified 432 donors with alpha-synuclein-immunoreactive pathology from the records of the Netherlands Brain Bank from the period 1982 to 2014. Patients were included if there was enough clinical information available to retrospectively diagnose them as PD, PDD or DLB according to current diagnostic criteria (N=135) and post-mortem tissue was available (final N=133). Thal phases for β -amyloidosis were assigned based on one section of the medial temporal lobe and, for a selection of cases (PD: N=24, PDD: N=34, DLB: N=31), the prevalence and load (=percentage of area) of A β pathology was assessed in nine cortical and subcortical regions. A multispectral imaging system was used for quantification.

Results and conclusion

Cholinergic cell density in the PPNc was significantly lower in PD, compared to DLB patients with VH (-39%, $p < 0.001$) and controls (-41%, $p < 0.001$). Alpha-synuclein load in the PPNc was higher in PD, whereas A β plaque pathology was more pronounced in DLB patients. In the second, larger cohort (N=133), we found higher Thal phases in DLB, compared to PDD patients ($p < 0.000$), and in PDD compared to PD patients ($p = 0.02$). Amyloid- β pathology was also more prevalent and, if present, a higher load was seen in multiple cortical and subcortical regions in DLB compared to PDD patients, and in PDD, compared to PD patients. In conclusion, our results indicate different patterns of degeneration of cholinergic output structures and concomitant A β pathology in PD, PDD and DLB. These neuropathological differences may contribute to the clinical differences between Lewy Body diseases, such as the development of VH and timing and presence of dementia.