Early Forms of α-Synuclein Pathology Are Associated with Neuronal Complex I Deficiency in the Substantia Nigra of Individuals with Parkinson's Disease

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Background

Idiopathic Parkinson's disease (iPD) is characterized by degeneration of the dopaminergic substantia nigra pars compacta (SNc), typically in the presence of Lewy pathology (LP) and mitochondrial respiratory complex I (CI) deficiency. LP is driven by α-synuclein aggregation, morphologically evolving from early punctate inclusions to Lewy bodies (LBs). The relationship between α-synuclein aggregation and CI deficiency in iPD is poorly understood. While studies in models suggest they are causally linked, observations in human SNc show that LBs preferentially occur in CI intact neurons. Since LBs are end-results of α-synuclein aggregation, we hypothesized that the relationship between LP and CI deficiency may be better reflected in neurons with early-stage α-synuclein pathology.

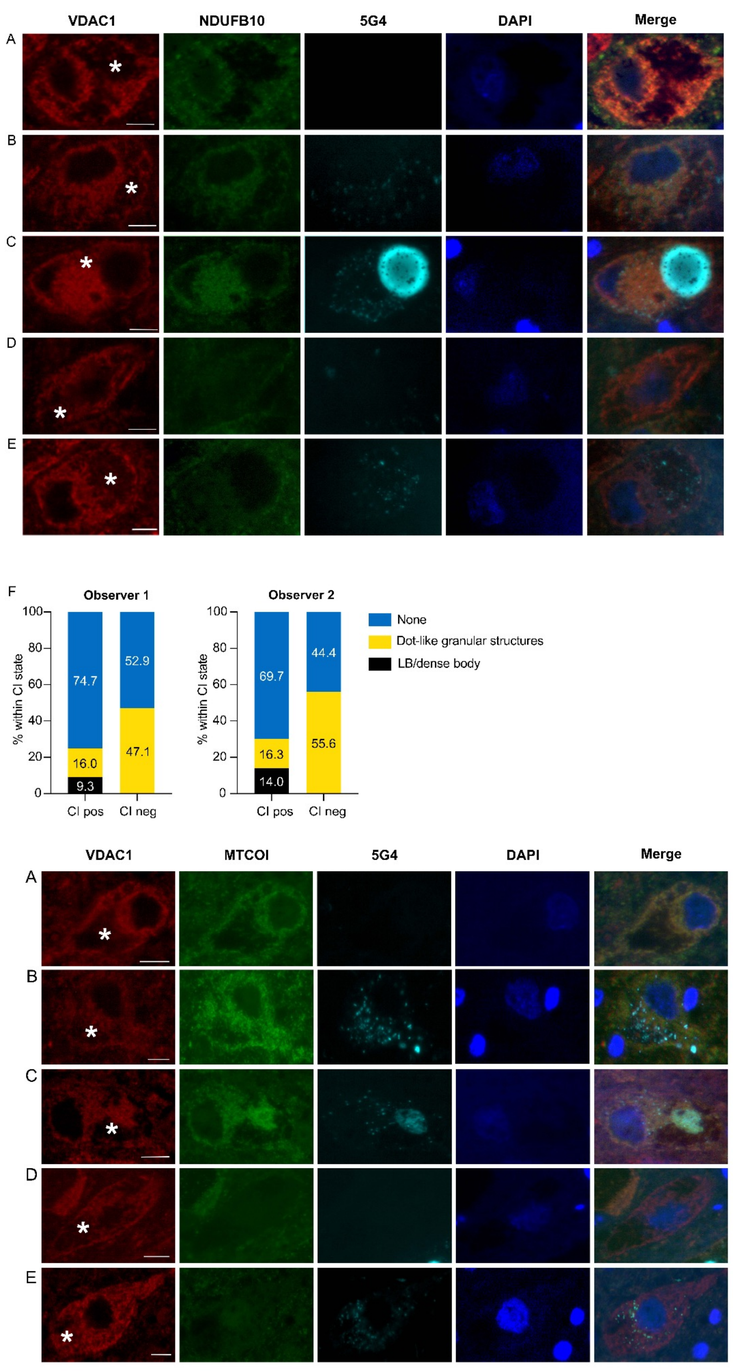
Materials and methods

The study was conducted on a population-based cohort of iPD (n=8) and neurologically healthy controls (n=5).

For the immunohistochemistry, 3-µm-thick sections were stained with primary anti- bodies against α-syn: clone 5G4; clone KM51. The clone 5G4 antibody shows a high immunoreactivity to all forms of ß-sheet rich α-syn aggregates and a lower affinity towards α-syn monomers, whereas the clone KM51 antibody recognizes full length α-syn.

We additionally did quadruple immunofluorescence staining with primary antibodies against the mitochondrial outer membrane protein VDAC1, α-syn 5G4 and mitochondrial CI, or mitochondrial CIV.

Results



There was a significant difference in the distribution of LP between CI-positive and CI-negative neurons ($p = 9.0 \times 10{-}4$, 99% C.I. ($1.3 \times 10{-}4$, 0.002)). We found no CI-negative neurons with LBs or PBs. Furthermore, we found that punctate inclusions showed a highly significant predilection for CI-negative neurons (CI-positive: 28/176, 16 %; CI-negative: 10/18, 56%; $p = 6.3 \times 10{-}5$). Conversely, there was a higher percentage of CI-positive neurons without LP compared to CI-negative neurons (CI-positive: 125/176, 71%; CI-negative: 8/18, 44%; $p = 0.021$)

CIV-negative neurons were observed in four to five of the six individuals, depending on the observer. Similar to the observation made in CI-negative neurons, we did not detect any LBs or PBs in CIV-negative neurons. Unlike the CI findings, however, there was no difference in the distribution of LP between CIV-positive and negative neurons (Fisher–Freeman–Halton Exact Test, $p = 0.44$).

Conclusion

In conclusion, our findings support a link between α-syn pathology and CI deficiency in the dopaminergic SNc of individuals with iPD. Specifically, our data suggest that early forms of LP have a strong predilection for CI deficient neurons. the combination of these two pathology states may drive neuronal loss, since late-stage LP appears to follow a reverse pattern, preferentially occurring in CI intact neurons.

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