HHS Public Access

Author manuscript

Lancet Neurol. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Lancet Neurol. 2020 January ; 19(1): 27–29. doi:10.1016/S1474-4422(19)30355-2.

Increased striatal dopamine in carriers of GBA mutations: compensation or epiphenomenon?

Nicolaas I. Bohnen, **Roger L. Albin**

Department of Radiology (NIB), and Department of Neurology, University of Michigan, University of Michigan Udall Center, and VA Ann Arbor Healthcare System (NIB, RLA), Ann Arbor, MI 48109, USA

LRRK2 and GBA mutations are common causes of genetic Parkinson's disease. Studies in non-manifesting carriers of these mutations provide the opportunity to investigate prodromal changes that could be relevant for understanding the pathophysiology of Parkinson's disease. Longitudinal studies in patients with rapid eye movement (REM) sleep behaviour disorder, at high risk for Parkinson's disease and other α-synucleinopathies, reveal an evolution of prodromal manifestations similar to that predicted by pathological staging models, with inferred prodromal intervals up to 20 years.[1] Studies of striatal dopamine transporter imaging in patients with REM sleep behaviour disorder have shown Parkinson's disease phenoconversion within 3 years in patients with severe deficits in striatal dopamine transporter binding.[2] A previous nigrostriatal terminal multi-tracer PET imaging study showed evidence of terminal losses in some non-manifesting carriers of LRRK2 mutations.[3] These patients might have maintained healthy motor function because of compensatory mechanisms—upregulation of dopa decarboxylase activity and downregulation of plasmalemmal dopamine transporters—maintaining normal concentrations of synaptic dopamine.

In The Lancet Neurology, Tanya Simuni and colleagues[4] report baseline clinical and dopamine transporter imaging results from a large cohort of LRRK2 (194 [93%] of 208 had the G2019S mutation) and GBA (177 [96%] of 184 had the N370S mutation) non-manifesting carriers. Non-manifesting carriers had mild but significantly increased number of decrements of motor, autonomic, and cognitive functions compared with healthy controls. 286 (73%) non-manifesting carriers had dopamine transporter imaging results. A surprising finding was that non-manifesting carriers of GBA mutations showed increased dopamine transporter striatal binding compared with LRRK2 mutant carriers and healthy controls. The authors suggest that high mean binding of striatal dopamine transporter in non-manifesting carriers of GBA mutations is a manifestation of a compensatory mechanism.

Given the mild motor features of non-manifesting carriers of GBA mutations, a compensatory process is a logical inference. However, increased binding of striatal dopamine transporter contradicts conventional ideas of compensatory mechanisms maintaining synaptic dopamine concentrations. Downregulation of expression of plasmalemmal dopamine transporter would be the expected response to diminishing synaptic

Corresponding author: nbohnen@umich.edu.

dopamine. Downregulation of presynaptic dopamine transporters will result in less dopamine reuptake in an attempt to preserve synaptic dopamine levels. Simuni and colleagues[4] discuss alternative explanations. One possibility is that synaptic dopamine concentrations are decreased in non-manifesting carriers of GBA mutations, leaving more dopamine transporter available for tracer binding. This alternative explanation seems incompatible with the partly preserved motor function in these non-manifesting carriers of GBA mutations. Another alternative is some form of compensatory sprouting of nigrostriatal terminals in an effort maintain nigrostriatal dopaminergic innervation, despite failing function of these terminals. Regenerative phenomena like this were suggested to occur in degenerating striatal neurons in Huntington's disease.[5] Another possibility is that increased expression of dopamine transporter is a secondary component of an overall compensatory process. Non-functional nigrostriatal dopaminergic neurons might exhibit increased dopamine synthesis, synaptic vesicle dopamine concentrations, and fractional release of synaptic vesicles with each depolarisation event. The result would be increased synaptic dopamine turnover, perhaps requiring further dopamine transporter expression as part of the overall compensatory process. Increased dopamine turnover might occur in some α-synuclein or adeno-associated virus models of Parkinson's disease.[6] A potential way to assess this possibility would be to measure concentrations of dopamine and its metabolite, homovanillic acid, in CSF. Elevated homovanillic acid to dopamine ratios would be consistent with increased synaptic dopamine flux and, if correlated with striatal dopamine transporter binding, would be evidence for this model of compensation.

Another likely explanation for the apparent upregulation of expression of plasmalemmal dopamine transporter is that increased binding of striatal dopamine transporter is a product of primary pathogenic processes in GBA Parkinson's disease, unrelated to dopamine transporter functions. A suggested mechanism of mutant GBA evoked neurodegeneration is α-synuclein accumulation and aggregation secondary to impaired lysosomal function.[7] α-Synuclein is abundant in synaptic terminals and interacts with important components of synaptic vesicle release and recycling mechanisms. Accumulation of α-synuclein in the nigrostriatal terminal is a plausible cause for alterations in dopamine transporter tracking.

The analysis is cross-sectional, limiting any inferences about functional correlates of changes in clinical features versus nigrostriatal nerve terminal changes. No CSF biomarkers of proteinopathy or neurotransmitter function were available for analysis. Differentiating whether the observed increase in striatal dopamine transporter binding in non-manifesting carriers of GBA mutations is a result of compensation or an epiphenomenon of primary pathogenesis might have important implications. If the increase is caused by the former, then understanding the mechanisms of compensation might lead to improved symptomatic therapies, and if caused by the latter, the epiphenomenon could provide useful information for exploring alternative pathogenetic mechanisms.

This study raises many questions. We agree with the investigators that their longitudinal data could provide important answers. Marked differences in dopaminergic and other biomarkers between non-manifesting carriers of GBA and LRRK2 mutations, and possibly between non-manifesting carriers of GBA mutations and in patients with REM sleep behaviour disorder, might indicate unique features of GBA pathophysiology. These findings provide a

strong reminder that Parkinson's disease is not a disease but a syndrome with multiple causes and probably multiple pathogenetic mechanisms.

Disclosures

NIB reports grants from the National Institutes of Health (P50 NS091856), Michael J Fox Foundation, Department of Veterans A airs, and Eisai, outside the submitted work. RLA declares no competing interests.

References

1. Fereshtehnejad SM, Yao C, Pelletier A, Montplaisir JY, Gagnon JF, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain 2019; 142: 2051–67. [PubMed: 31111143]
2. Iranzo A, Valldeoriola F, Lomena F, et al. Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. Lancet Neurol 2011;?10: 797–805. [PubMed: 21802993]
3. Adams JR, van Netten H, Schulzer M, et al. PET in LRRK2 mutations: comparison to sporadic Parkinson's disease and evidence for presymptomatic compensation. Brain 2005; 128: 2777–85. [PubMed: 16081470]
4. Simuni T, Uribe L, Cho HR, et al. Clinical and DAT imaging characteristics of non-manifest LRRK2 and GBA mutation carriers in the Parkinson's Progression Markers Initiative: a cross sectional study. Lancet Neurology 2019; published online 10 30 10.1016/S1474-4422(19)30319-9.
5. Graveland GA, Williams RS, DiFiglia M. Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. Science 1985; 227: 770–73. [PubMed: 3155875]
6. Koprich JB, Johnston TH, Huot P, Reyes MG, Espinosa M, Brotchie JM. Progressive neurodegeneration or endogenous compensation in an animal model of Parkinson's disease produced by decreasing doses of alpha-synuclein. PloS One 2011; 6: e17698. [PubMed: 21408191]
7. Ryan E, Seehra G, Sharma P, Sidransky E. GBA1-associated parkinsonism: new insights and therapeutic opportunities. Curr Opin Neurol 2019;?32: 589–96. [PubMed: 31188151]