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Hypercholinergic activity in LRRK2 Parkinson's disease

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Mutations of the leucine-rich repeat kinase 2 (LRRK2) gene are a common cause of autosomal dominant Parkinson's disease. The clinical features of manifest LRRK2 Parkinson's disease are generally indistinguishable from those of sporadic Parkinson's disease though some features may be less prominent, including less hyposmia and less cognitive decline.¹ Study of pre-manifest LRRK2 Parkinson's disease has the potential to identify early, important events in Parkinson's disease pathophysiology and pathogenesis. Cholinergic system changes are implicated in a number of non-motor features of idiopathic Parkinson disease.²

In this issue, Liu *et al.* report *in vivo* imaging of cerebral cholinergic synapses with acetylcholinesterase positron emission tomography in pre-manifest and manifest LRRK2 Parkinson's disease in comparison with idiopathic Parkinson's disease and controls.³ Pre-manifest LRRK2 Parkinson's disease subjects had increased cortical acetylcholinesterase activity compared to control subjects. Manifest LRRK2 Parkinson's disease subjects had significantly higher acetylcholinesterase activity in cortical and thalamic regions compared to idiopathic Parkinson's disease subjects.

Increased acetylcholinesterase activity may reflect increased neurotransmission within cortical and thalamic cholinergic synapses. Cortical hypercholinergic activity in pre-manifest LRRK2 Parkinson's disease is compatible with increased basal forebrain corticopetal cholinergic neuron activity compensating for striatal dopaminergic dysfunction.⁴ This group suggested previously that pre-manifest LRRK2 Parkinson's disease exhibits compensatory increases in striatal dopaminergic neurotransmission.⁵ Moreover, it is plausible that Liu and colleagues current findings of amplified acetylcholinesterase activity could reflect a compensatory response to failing cholinergic projection neurons, as suggested to occur in Alzheimer's disease.⁶ These results suggest differences in the pathophysiology of LRRK2 and idiopathic Parkinson's disease.

Manifest LRRK2 Parkinson's disease subjects had significantly higher depression ratings and trends toward lower cognitive ratings and greater motor dysfunction than the idiopathic Parkinson's disease group. The range of cortical and thalamic acetylcholinesterase activity in the manifest LRRK2 Parkinson's disease subjects was wider than found in the idiopathic Parkinson's disease group. Greater variation in acetylcholinesterase activity suggests

underlying heterogeneity with some subjects exhibiting increased and others decreased acetylcholinesterase activity. LRRK2 Parkinson's disease is genetically, pathologically, and clinically heterogeneous. Some LRRK2 Parkinson's disease mutations lack Lewy bodies and exhibit a predominantly motor dysfunction phenotype with less non-motor features.¹ G2019S mutation carriers may score higher in motor scores while R1441G carriers may have higher non-motor scores.⁷ The 14 manifest LRRK2 Parkinson's disease subjects studied had 3 different mutations. It is plausible that different mutations have different effects on cholinergic systems. The small sample size of this study precludes sub-group analysis but expanded genotype-phenotype correlations could be interesting.

Liu and colleagues discuss another interesting explanation for their findings. As they point out, acetylcholine may be an important regulator of microglial function. Microglial cells express $\alpha 7$ nicotinic cholinergic receptors whose activation attenuates the pro-inflammatory response of microglial cultures, suggesting that acetylcholine may regulate brain inflammation.⁸ While retention of this radioligand mainly reflects acetylcholinesterase activity, it may also reflect butyrylcholinesterase activity, which may play an important role in modulating neuroinflammation.⁸ The increased tracer retention documented by Liu *et al.* may be driven by increased cholinergic neurotransmission, activation of microglia, or both.

Liu *et al.* set the stage for potentially important explorations of compensatory mechanisms and pathogenesis in both LRRK2 and idiopathic Parkinson's disease. Exploration of potential changes in compensatory cholinergic systems changes might identify new targets for symptomatic therapies. Elucidation of cholinergic functions in neuron-microglial interactions may provide a novel framework to investigate inflammatory processes in neurodegeneration. Longitudinal studies with detailed clinical, neuro-inflammatory, and cholinergic biomarker assessments may help to disentangle this complex interaction.

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