

# Preventing Parkinson disease by vagotomy

## Fact or fiction?

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Aggregation of the neuronal protein  $\alpha$ -synuclein into insoluble filamentous inclusions may be a determining factor in the development of Parkinson disease (PD). Converging evidence has demonstrated that  $\alpha$ -synuclein inclusions have prion-like properties, including cell-to-cell transmission and the ability to induce native  $\alpha$ -synuclein to misfold, thus setting the stage for domino-like spreading of cellular pathology.<sup>1</sup>

The postmortem literature is generally compatible with the Braak hypothesis, i.e., that  $\alpha$ -synuclein pathology in PD initially occurs in the anterior olfactory nucleus and the dorsal motor nucleus of the vagus.<sup>2</sup> Because these neuronal structures are connected to the outside world, one could hypothesize that PD pathology might originate with or be aggravated by exterior insults that activate nerve terminals in the olfactory epithelium and gastrointestinal lining.<sup>3</sup>

Early involvement of the gastrointestinal tract is supported by evidence that a substantial fraction of patients with PD develop constipation years or even decades before motor symptoms.<sup>4</sup> In addition,  $\alpha$ -synuclein inclusions may be found in gastrointestinal nerve endings up to 20 years before diagnosis.<sup>5</sup> Finally, in a transgenic rodent model of PD, intraperitoneal injections of  $\alpha$ -synuclein fibrils led to  $\alpha$ -synucleinopathy throughout the CNS and severe neurologic symptoms within several months.<sup>6</sup> However, direct evidence for the postulated peripheral-to-central spreading in human patients with PD is limited.

If the vagus nerve is indeed a major route for centripetal  $\alpha$ -synuclein propagation, severing this structure (e.g., surgical vagotomy) could theoretically be protective against the development of PD. In this issue of *Neurology*®, Liu et al.<sup>7</sup> used nationwide Swedish registries to test this hypothesis. Compared to 377,200 control individuals, patients treated with truncal vagotomy for peptic ulcer showed a decreased risk for developing PD after >5 years (hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.37–0.93). An important finding is

that patients treated with this procedure had a lower PD risk than those treated with selective vagotomy (HR 0.54, 95% CI 0.32–0.91). In contrast to complete transection of the nerve trunk, selective procedures spare the celiac and hepatic branches, denervating only the corpus and fundus of the stomach.

In 2015, a Danish registry study was the first to test the purported protective effects of vagotomy in PD.<sup>8</sup> In that study, patients undergoing selective vagotomy were binned with those receiving truncal vagotomy because of concerns of registry code validity. Only patients treated with superselective vagotomy could be isolated. Although the statistical power of that study might have been diminished, a similar protective effect of truncal/selective vagotomy was detected (HR 0.53, 95% CI 0.28–0.99). The importance of those findings did not escape the attention of the PD research community. However, caution was recommended regarding its conclusions, and the need for replication of the findings by independent groups was advised.

The current study by Liu et al.<sup>7</sup> provides an independent dataset suggesting that truncal vagotomy may be protective in PD. Therefore, the time has come to seriously consider the implications of these findings. Could it be true that  $\alpha$ -synuclein misfolding in PD may originate in the autonomic nerve terminals of the gastrointestinal tract?

For the moment, more research is needed. Work in animal models could elucidate the spatial-temporal spreading patterns of pathologic  $\alpha$ -synuclein propagation and whether and to what degree vagotomy delays spreading to the CNS. Improved methods to define and detect pathologic  $\alpha$ -synuclein inclusions in peripheral organs are also required.<sup>9</sup> Such methods should be investigated in whole-body autopsies of patients with incidental Lewy body disease and Lewy-negative reference cases. Ultimately, such studies may help to establish whether  $\alpha$ -synucleinopathy, perhaps in its oligomeric form, can be detected in the gastrointestinal tract before CNS involvement. Similar studies could be carried out on

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archived tissue specimens removed from patients with PD before diagnosis.

Does truncal vagotomy hold potential as a therapeutic intervention for PD? Probably not in the majority of cases. Recently, much effort has been put into the accurate prediction of who will develop PD, particularly motor symptoms.<sup>10</sup> The strongest predictive factors to date are the presence of REM sleep behavior disorder and dopamine terminal imaging deficits. When these symptoms and deficits appear, it is already too late because neurodegenerative pathology is widespread throughout the brainstem.

Nevertheless, one may consider studying the effects of vagotomy in patients with mutations in the leucine-rich repeat kinase-2 gene (*LRRK2*), which dramatically increases the risk of developing neurodegenerative parkinsonism. Some of these mutations have a penetrance of up to 80% in the very elderly. However, it is largely unknown whether  $\alpha$ -synuclein aggregates are present in gastrointestinal nerve endings of these patients. At this stage, we have insufficient knowledge to propose vagotomy as a putative treatment for PD.

Finally, if the initial  $\alpha$ -synuclein aggregation happens in the gastrointestinal lining, what triggers this misfolding event? Although vagotomy will likely never become a widespread treatment for PD, strategies to prevent  $\alpha$ -synuclein misfolding in the gastrointestinal tract may be proposed because nerve terminals are reachable by oral therapeutic interventions.

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#### DISCLOSURE

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#### REFERENCES

1. Goedert M, Masuda-Suzukake M, Falcon B. Like prions: the propagation of aggregated tau and alpha-synuclein in neurodegeneration. *Brain* 2017;140:266–278.
2. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.
3. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. *Neuropathol Appl Neurobiol* 2007;33:599–614.
4. Adams-Carr KL, Bestwick JP, Shribman S, Lees A, Schrag A, Noyce AJ. Constipation preceding Parkinson's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016;87:710–716.
5. Stokholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological alpha-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. *Ann Neurol* 2016;79:940–949.
6. Breid S, Bernis ME, Babila JT, Garza MC, Wille H, Tamguney G. Neuroinvasion of alpha-synuclein prionoids after intraperitoneal and intraglossal inoculation. *J Virol* 2016;90:9182–9193.
7. Liu B, Fang F, Pedersen NL, et al. Vagotomy and Parkinson disease: a Swedish register-based matched-cohort study. *Neurology* 2017;XX:xxx–xxx.
8. Svensson E, Horvath-Puho E, Thomsen RW, et al. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015;78:522–529.
9. Corbille AG, Letournel F, Kordower JH, et al. Evaluation of alpha-synuclein immunohistochemical methods for the detection of Lewy-type synucleinopathy in gastrointestinal biopsies. *Acta Neuropathol Commun* 2016;4:35.
10. Berg D, Postuma RB, Adler CH, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 2015;30:1600–1611.