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PARKINSON DISEASE

Peripheral α-synuclein deposits — prodromal markers for Parkinson disease?

> submandibular gland α-synuclein could be a diagnostic marker of PD

Evidence is mounting that the pathophysiological process that culminates in a diagnosis of Parkinson disease (PD) initiates in the autonomic nervous system, possibly many years before the classic motor symptoms emerge. Two new studies show that pathological aggregates of the PD-associated protein α-synuclein are detectable in the gastrointestinal tract and submandibular glands during the prodromal stage of PD, thereby lending support to this idea.

Morten Stokholm and colleagues used immunohistochemistry to screen for the presence of α-synuclein deposits in the gastrointestinal tract during the prodromal phase of PD. Their study included 57 patients with PD — 39 of whom had gastrointestinal tissue samples taken before diagnosis of PD — and 90 healthy controls.

"We chose two techniques that visualize the kind of α-synuclein that is associated with PD pathology," explains Stokholm. "One technique visualized aggregated α-synuclein, which has been associated with degeneration of dendritic spines in striatal neurons, and the second utilized an antibody against phosphorylated α-synuclein, which is present at high concentrations in Lewy bodies — a pathological hallmark of PD."

Stokholm's team detected gastrointestinal deposits of phosphorylated α-synuclein in 56% of individuals with prodromal PD, compared with 26% of controls. The rates of positivity for aggregated α-synuclein, however, were comparable between patients with prodromal PD and controls. Interestingly, phosphorylated α-synuclein could be detected in the gastrointestinal tract up to 20 years before a definitive diagnosis of PD.

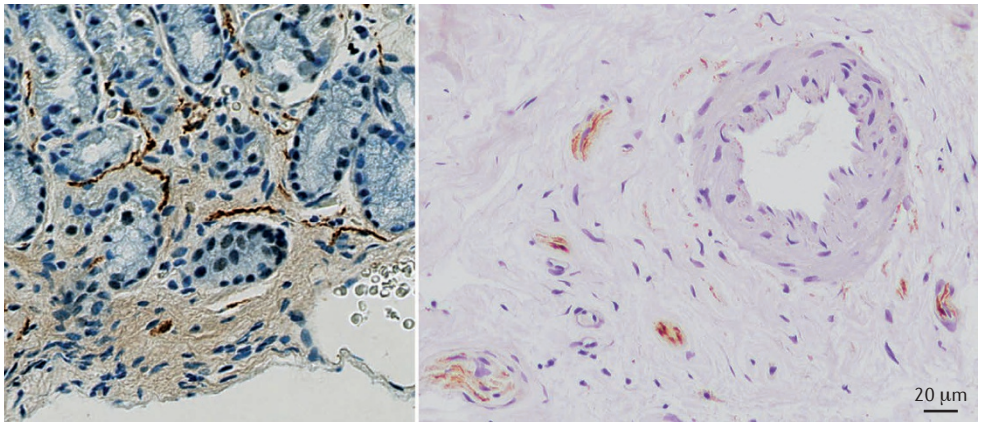
"At the moment, the relevance of pathological α-synuclein deposition in the gut of healthy control individuals is unknown," comments Stokholm. "Does its presence predispose to the development of PD, or is it a benign phenomenon?"

The second study, by Eduardo Tolosa and co-workers, focused on individuals with idiopathic REM sleep behaviour disorder (IRBD) — a parasomnia that is characterized by dream-enacting behaviours and is frequently observed as a nonmotor precursor to PD. The researchers used an immunohistochemical technique to search for aggregated α-synuclein in submandibular gland tissue samples obtained by biopsy.

"α-Synuclein aggregates were detected in nerve fibres of the glandular parenchyma in eight of nine patients with IRBD and eight of 12 patients with PD, but none of the controls," reports Tolosa. "Our studies confirm that submandibular gland α-synuclein could be a diagnostic marker of PD, and might be used for the selection of candidates for disease modification trials in the prediagnostic phase of PD." The results also help to reinforce the proposed pathological link between IRBD and PD.

Both of the research teams are planning to refine their techniques and confirm their findings in larger patient cohorts. In addition, Tolosa suggests that future studies should include individuals with PD-like conditions such as progressive supranuclear palsy or multiple system atrophy, so as to determine the specificity and sensitivity of peripheral α-synuclein aggregates as a prediagnostic marker for PD.

Heather Wood



Pathological α-synuclein deposits in pylorus tissue from a patient with prodromal PD (left panel) and the submandibular gland of a patient with REM sleep behaviour disorder (right panel). Images courtesy of M. G. Stokholm and Ellen Gelpi (via E. Tolosa).

ORIGINAL ARTICLES Stokholm, M. G. *et al.* Pathological alpha-synuclein in gastrointestinal tissues from prodromal Parkinson's disease patients. *Ann. Neurol.* http://dx.doi.org/10.1002/ana.24648 (2016) | Vilas, D. *et al.* Assessment of α-synuclein in submandibular glands of patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case–control study. *Lancet Neurol.* http://dx.doi.org/10.1016/S1474-4422(16)00080-6 (2016)

FURTHER READING Klingelhoefer, L. & Reichmann, H. Pathogenesis of Parkinson disease — the gut–brain axis and environmental factors. *Nat. Rev. Neurol.* **11**, 625–636 (2015)