Does REM sleep behavior disorder have the guts to be Parkinson disease?

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Neurology® 2015;85:1732–1733

Almost 200 years ago, James Parkinson[1] described constipation as a frequent and clinically relevant nonmotor symptom in shaking palsy. Recent studies have shown that constipation can precede the motor manifestation of Parkinson disease (PD)[2,3] and that constipation is more frequent in idiopathic REM sleep behavior disorder (iRBD) (a potential prodromal stage of PD) compared to controls.[4] Even though the causal relationship between constipation and the neurodegenerative process that underlies PD remains debatable, constipation is considered as a risk marker for a subsequent diagnosis of PD.[3] One potential pathoanatomical correlate for constipation in PD is Lewy bodies, the pathohistologic hallmark of PD, in the enteric nervous system (ENS). Lewy body pathology is found throughout the gastrointestinal tract with a rostral to caudal gradient. While early work on Lewy body pathology in the ENS was postmortem,[5] recent studies have shown that the ENS is also easily amenable to in vivo pathohistologic assessment using endoscopy.[6,7] The presence of ENS Lewy body pathology in PD led to the hypothesis that the ENS might be one of the first sites where Lewy body pathology occurs in PD.[8] Few in vivo data exist on ENS pathology in early-stage PD.

In this issue of *Neurology*®, Sprenger et al.[9] report on immunoreactivity to α-synuclein (one major component of Lewy bodies) in the ENS of patients with iRBD, patients with PD, and controls. iRBD is considered one of the most specific prodromal markers of PD. Sprenger et al. collected colonic biopsies and analyzed the specimens using 2 different antibodies for α-synuclein. Immunostaining with an antibody that binds to native α-synuclein (15G7 antibody) showed a similar pattern of immunoreactivity in controls, patients with iRBD, and patients with PD. Hence, immunostaining with the 15G7 antibody did not differentiate between patients and controls due to nonspecific binding to α-synuclein, which is a ubiquitous neuronal protein. In contrast, submucosal immunostaining with the pSyn antibody that binds to phosphorylated α-synuclein was negative in all controls, but positive in 4 out of 17 patients with RBD and 1 out of 19 patients with PD.

ENS immunoreactivity with the pSyn antibody solely in patients with iRBD and patients with PD indicates a probable specificity for α-synculeinopathies, but considering the number of positive cases, the sensitivity to detect an α-synculeinopathy with this technique seems to be low. The authors discuss explanations for the low rate of yield in the context of divergent observations in other studies. Considering divergent data on the specificity of α-synuclein immunoreactivity in the ENS, one strength of the work by Sprenger et al. is the use of 2 different antibodies. The results indicate that methodologic aspects, including the selection of the antibody, processing of the specimens, and depths of biopsies (mucosal vs submucosal tissue), are crucial for the robustness and interpretation of the data.

Despite the lack of statistical significance and despite the fact that colonic biopsies will not be readily applicable as a diagnostic biomarker for prodromal PD, the study by Sprenger et al. is of notable importance. The novel observation of α-synuclein immunoreactivity (with the pSyn antibody) in the ENS of some patients with iRBD, one patient with PD, but none of the controls endorses the link between iRBD and PD and supports the hypothesis of a common pathology in both disorders. The results are compatible with current concepts of an early pathology in the ENS in PD (and iRBD) and imply that PD-related pathology might be detectable in vivo at a prodromal stage.

Longitudinal studies will be required to clarify the import of positive ENS biopsies in iRBD, i.e., whether there are differences between patients with iRBD with positive and negative immunostaining with regard to the natural course or clinical characteristics.

At present, it remains to be shown whether refinement of this approach (in terms of histologic techniques, number and optimal site of biopsies, repeated endoscopies, and combination with other markers) will be able to increase the hit to miss ratio and finally

See page 1761

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

result in an in vivo biomarker for early or prodromal PD. In consideration of the rostral to caudal gradient of Lewy body pathology in the ENS,[10] gastric mucosa specimens (instead of or in combination with colonic biopsies) might be another promising option to detect PD-related pathology in the ENS in vivo.

The involvement of the gastrointestinal tract in early PD is generally accepted; its relevance for clinical care as well as for understanding the pathology is widely recognized. Yet it remains a challenging task to clarify the causality and chronology among symptoms, signs, and histologic findings in the gastrointestinal tract and the neurodegenerative process in PD.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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