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Pure autonomic failure vs. manifest CNS synucleinopathy: Relevance of stridor and autonomic biomarkers

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on behalf of On behalf of the Autonomic Disorders Consortium**

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We thank Drs. Silber, Boeve, and St. Louis for their comments on our recent paper describing the natural history of pure autonomic failure (PAF)¹.

We agree that rapid eye movement (REM) sleep behavior disorder (RBD) indicates that CNS neurons are *already* affected, and thus the disease is not exclusively autonomic and is likely to progress. This is also the case with hyposmia. Indeed, in the discussion we suggest, *“the presence of RBD, olfactory loss, and subtle motor deficits should be considered as non-supportive features of PAF.”*

We use the term “manifest” (meaning clear or obvious) CNS synucleinopathy to refer to the clinical evolution into the motor/cognitive stage when patients reach a full diagnosis of Parkinson disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA).

Thus, we want to emphasize that many patients with an initial diagnosis of PAF *do* indeed have CNS involvement. In such cases, they cannot be considered as suffering from an isolated peripheral autonomic nerve disorder, as our study shows that this is a pre-motor/pre-cognitive stage.

When we reviewed the detailed clinical histories of the PAF cohort, we did not find evidence of nocturnal stridor in the pre-motor autonomic phase. Although there are rare cases when nocturnal stridor was reported as the presenting feature of MSA^{2–4} our data and previous reports,⁵ suggest that this is infrequent (< 5%). Nevertheless, we are paying close attention to the appearance of stridor in our cohort.

Finally, we agree with Drs. Silber, Boeve, and St. Louis on the need to update the consensus diagnostic criteria for MSA to take into account the results of our study. After all, autonomic dysfunction, RBD, and hyposmia have been proposed as key features of prodromal PD in recent consensus diagnostic criteria.⁶ We believe that patients with RBD, autonomic

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biomarkers, and *intact* olfactory function, with or without stridor should be considered as having pre-motor MSA.

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