Reply to: Autonomic dysfunction in Parkinson's disease: the hidden game changer?

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Word count: 484

Running Title: Reply to autonomic dysfunction in PD

Keywords: Parkinson's disease; Autonomic; Orthostatic Hypotension; Supine Hypertension

Financial disclosure related to research covered in this article

All the authors have nothing to declare

Funding sources

Nothing to declare

We thank Drs. De Pablo-Fernandez and Warner for their insightful letter regarding our recent prospective cohort study on autonomic dysfunction in Parkinson disease (PD) [1]. We agree with our colleagues that there is a major challenge in the accurate recognition of PD from multiple system atrophy (MSA) as autonomic dysfunction can be an early and prominent clinical feature in both disorders whereas motor features may be initially indistinguishable between them.

We cannot exclude the possibility that some of the patients in our cohort may have had MSA or, conversely, that some PD patients had been erroneously misdiagnosed as MSA and therefore excluded from this cohort due to early autonomic dysfunction. However, a review of our data showed that 37/104 (35.6%) of patients included in our cohort had early autonomic impairment, suggesting that the latter possibility, if not fully ruled out, is improbable.

We do agree that autonomic dysfunction represents one of “the hidden game changers in PD" since it is an under-recognized and, therefore, under-treated source of PD disability, particularly orthostatic hypotension (OH). For instance, a phase-III, randomized, placebo-controlled, double-blind clinical trial of 224 non-demented PD patients with OH showed a reduction in the rate of falls by 295% over an 8-week observational period in those receiving droxidopa compared to placebo [2]. In a chart review of 316 PD patients, we found that OH increased health care utilization independently from age, disease duration, motor severity, dopaminergic treatment, and cognitive function [3]. Importantly, even “asymptomatic” OH (i.e., not endorsing postural lightheadedness) yields similar impairment in quality of life and rate of falls than symptomatic

OH [4], suggesting that traditional screening questionnaires may not be sufficient to uncover this treatable complication.

Multiple studies, including the recent publication from De Pablo-Fernandez and colleagues, "Association of Autonomic Dysfunction with Disease Progression and Survival in Parkinson Disease", have shown that autonomic dysfunction may affect patients with PD from the very early stages or even in pre-motor stages [5]. In that publication, the authors further noted that earlier appearance of autonomic dysfunction increased the risk of reaching milestones of PD disability and shortened survival despite the lack of correlation with α-synuclein pathologic staging. While confirming the key role of dysautonomia as a determinant of functional disability in PD, this data suggest that our current pathological model fails to recapitulate the complexity of autonomic dysfunction involved in the dysautonomia of MSA and PD.

In conclusion, we agree with the central premise from De Pablo-Fernandez and Warner that “the possibility of either clinical misdiagnosis or inappropriate exclusion of patients must be considered in design and data interpretation, as it may lead to potential bias affecting the conclusions of the study”. We also advocate for the institution of a cohort employing comprehensive autonomic assessments, as well as skin biopsies, peripheral biomarkers, and autopsy material to assist the next generation of biomarker development efforts and, ultimately, ushering the era of precision medicine in PD.

ACKNOWLEDGMENT

Authors acknowledge the contributions of the Neurology Unit staff at the San Giovanni Battista Hospital, Turin and the Medical Arts Building at the University of Cincinnati.

AUTHORS' ROLES

1) Project: A. Conception; B. Organization; C. Execution

2) Analysis: A. Design; B. Execution; C. Review and Critique

3) Manuscript Preparation: A. Writing of the first draft; B. Review and Critique

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All the co-authors listed above gave their final approval of this manuscript version.

FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

Aristide Merola: he is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Cynapsus Therapeutics, and AbbVie. He has received grant support from Lundbeck and Abbott; Alberto Romagnolo: grant support and speaker's honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco and UCB Pharma; Leonardo Lopiano: has received honoraria for advisory board, lecturing and travel grants from AbbVie, UCB, Zambon, Chiesi, Medtronic, Doc, Allergan, Bial; Alberto J Espay: he

has received grant support from the NIH, Great Lakes Neurotechnologies and the Michael J Fox Foundation; personal compensation as a consultant/scientific advisory board member for Abbvie, TEVA, Impax, Acadia, Acorda, Cynapsus/Sunovion, Lundbeck, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from Abbvie, UCB, USWorldMeds, Lundbeck, Acadia, the American Academy of Neurology, and the Movement Disorders Society.

DATA ACCESS AND RESPONSIBILITY STATEMENT

A. Merola and A. Romagnolo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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