Author’s response to reviews

Title: Association between autonomic dysfunction and olfactory dysfunction in Parkinson’s Disease in southern Chinese

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Author’s response to reviews:

Dear Prof. Kwon,

Please find our revised manuscript entitled “Association between autonomic dysfunction and olfactory dysfunction in Parkinson’s Disease in southern Chinese”(ID: NURL-D-18-00631) to be considered for publication as an article in BMC Neurology. We really appreciate the constructive comments from reviewers and editor. We have revised our manuscript according to reviewers’ suggestions with highlight in the manuscript and answered all the questions raised point by-point as below. Hope our revised manuscript meets the published standards of your journal.

We thank you in advance for considering our revised manuscript.

Best regards,

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Reviewer reports:

Jinse Park (Reviewer 1): This study is for investigating association between hyposomia and non-motor symptoms in PD. This topic is novel and study design is concise, but several major concerns were existed.

Introduction

- I wonder why author would investigate the association between olfactory dysfunction and autonomic dysfunction. Is there a clinical meaning or pathological importance? Or Is there a previous report that olfaction and dysautonomia are linked with each other? The more exact background and purpose of this study should be described.

Response: Thanks for your comments. Both olfactory dysfunction and several autonomic dysfunctions such as constipation present prodromal biomarkers for PD with peripheral origins. But rare studies focused on their relationships in PD patients. The differences of autonomic dysfunction of PD patients with olfactory dysfunction and without olfactory dysfunction are rarely discussed. So in this article, we try to discover their relationships from the perspective of differences between PD patients with olfactory dysfunction and PD patients without olfactory dysfunction. We supplemented that in Introduction Part. Thanks.

Method

- In my opinion, independent t-test is not proper method to compare between two groups (with olfactory dysfunction, without olfactory dysfunction). Like correlation, Statistical adjusting confounding factors including disease duration, severity and age seems to be necessary.

Response: Thanks for your comments. We think it is necessary to adjusting those confounding factors. We adjusted age, gender, disease duration and Hoehn – Yahr staging. There were no correlations between age and disease duration (p = 0.721). The p value of total SCOPA-AUT was 0.008. As for subparts, p values of gastrointestinal symptoms, urinary symptoms, cardiovascular symptoms, skin symptoms, sexual symptoms and drug usage were 0.024, 0.008, 0.076, 0.793, 0.804 and 0.783 perspectively. We corrected those in Table 1 and results part. Thanks.

- Why author set gender as the confounding factor? I think age is more important factor to olfactory dysfunction.

Response: Thanks for your comments. We adjusted gender because gender was not perfectly matched in our demographic data at first. When re-calculated that after adjusting age, gender and disease duration. We corrected those data in Table 2 and results part. Thanks.

- How author exclude the patients with dementia? Inclusion or exclusion criteria did not consider cognition. Olfactory dysfunction is also common in dementia including Alzheimer disease as well as Parkinson's disease.


Response: Thanks for your comments. In our clinics, normal MMSE and MoCA scores were necessary when we assessed patients since there were AD, DLB and PDD groups. PD patients without dementia and hallucinations were mandatory when we selected since they would interfere the whole tests. We added relevant information in the “Study Population” of Methods part. Thanks.

Discussion

- In discussion section, there are lack of explanation or hypothesis about the relation between olfaction and autonomic dysfunction. How can we interpret the correlation between olfaction and constipation, urinary function?

Response: Thank you for your comments. There was maybe more global involvement in non-motor symptoms in PD. Environmental factors, such as microbiological changes, may influence PD non-motor symptoms and pathogenesis of PD given the anatomical position of organs with olfactory function, constipation and urinary functions. More studies to discover the pathogenesis of environmental factors to PD are warranted. We added that in Discussion part. Thanks.

- How the author conclude causal relationship between olfactory dysfunction and constipation? Olfaction is particularly important in eating and nutrition. It can be possible that olfactory dysfunction cause poor oral intake and lead to constipation. Additional factor for nutrition such as Dietary habit, body mass index should be offered.

Response: Thank you for your comments. Our patients were balanced dietary habit given from their caregivers. Their dietary habit was not changed. BMI in PD patients with olfactory
dysfunction was 22.19 ± 2.11 (mean ± SD). BMI in PD patients without olfactory dysfunction was 22.42 ± 2.46 (mean ± SD). The p value was 0.631, which indicated that there was no difference between two groups. Environmental factors, such as microbiological changes, may influence olfactory dysfunction and constipation. More studies to discover the pathogenesis of environmental factors to PD are warranted. We added that in results part. Thanks.

- "The strength of our study are that all PD patients enrolled in our study were from outpatient’s clinic" - Why enrollment from outpatients clinic is "strength" in this study?

Response: Thank you for your comments. We meant to emphasize our patients were randomly tested. PD patients in our ward are usually accompanied with severe complications or evaluated for deep brain stimulation. That sentence brought ambiguity and we deleted that since it was not necessary. Thanks.

Jongkyu Park, M.D. (Reviewer 2): Because Hyposmia is a common symptom of Parkinson's disease, the accuracy of the diagnosis is important if the patient has Parkinson's disease without hyposmia. Additional explanations are acceptable to the reader, and it would be nice to attach DAT scan results and LEDDs.

Overall, the rate of GI, uninary, and cardiovascular symptom was high in PD with hyposmia, which is similar to that seen in MSA-P patients(https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0180744), and it is necessary to confirm that PD patients are completely excluded from MSA-P patients. It would be better to exclude H & Y stage 4 patients who are progressing faster than 7.86yrs Disease duration.

Response: Thank you for your comments. Indeed, MSA-P patients are easily misdiagnosed by PD. In this study, the diagnosis was made by two different movement disorder specialists to confirm the diagnosis. They presented PD symptoms rather than MSA-P, such as significantly responsive to levodopa. Some patients were performed 18F-FDG PET from other hospitals when they came to our clinics.