Author’s response to reviews

Title: A survey of subjective constipation in Parkinson's disease patients in Shanghai and literature review

Authors:
Jing Gan (ganjing@xinhuamed.com.cn; ganjing67@126.com)
ying Wan (wanying@xinhuamed.com.cn)
Junjie Shi (cynthia714@126.com)
Mingzhu Zhou (estherzhoumz@aliyun.com)
Zhiyin Lou (louzhiyin@xinhuamed.com.cn)
zhenguo liu (liuzhenguo@xinhuamed.com.cn)

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A survey of subjective constipation in Parkinson's disease patients in Shanghai and literature review

Jing Gan, Ph.D M.D; ying Wan; Junjie Shi; Mingzhu Zhou; Zhiyin Lou; Zhenguo Liu

BMC Neurology

Reviewer reports:

Yi-Cheng Tai (Reviewer 1): Abstract

Line 2: "… and the prevalence in PD patients varies from different studies" should be "… and the prevalence of constipation in PD patient varies with different studies"

Thanks for the reviewer. We have changed in the text.
... and the chronology of appearance of constipation onset in relation to onset of motor symptoms in PD patients from Shanghai, China"

Does it mean "... and duration between the emergence of constipation and the onset of motor symptoms in PD patients from Shanghai, China"

Yes. We have changed.

"Among them, there was 47.59% patients ....." please delete the word "patients"

Thanks for the reviewer. We have changed.

"and were easier to accompany with anxiety, depression and insomnia." Should be " and were prone to have ......"

Thanks for the reviewer. We have changed.

"The lead-time of constipation to motor onset (6.62±9.32) years." Does it means "The time span between the constipation and the onset of motor symptoms was 6.62±9.32) years"

Yes. In the PD patients with pre-motor constipation group, the time span between the constipation and the onset of motor symptoms was (6.62±9.32 years).

Please explain "Total timespan from earliest initial symptoms to present was similar"

According to our data, if we regard constipation as one initial symptoms of PD, disease duration in ‘constipation pre-motor signs’ group would be changed with data of ‘duration of constipation’. It was (10.33±10.13) years. The disease duration of ‘constipation post-motor signs’ group was (8.50±4.66) years. There was no difference between duration of constipation in ‘constipation pre-motor signs’ group and duration of motor signs in ‘constipation post-motor signs’ group.
(t=1.367, p=0.175) (Fig 1B). We want to say that the time interval from the earliest initial symptoms (motor symptom or constipation) to present was similar between these two groups. It might be suggested that constipation was one part of PD or a manifestation of early PD.

Line 15: "Patients with pre-motor constipation presented motor signs at an older age, manifested less serious parkinsonian symptoms, more severe constipation and took less levodopa." Please correct the grammar.

Thanks for the reviewer. We have changed.

Background

Line 41: This may be the reason why there was variation of constipation prevalence and this is not helpful to characterize this NMS." Please mind the tense.

Thanks for the reviewer. We have changed.

Line 46: "Recently, one systematic review and meta-analysis proved that people with constipation have a higher risk of developing PD compared with those without." Please cite the reference

Thanks for the reviewer. We have cited the reference.

Methods

Please define "with constipation" and "without constipation"

Thanks for the reviewer. We have added the definition in the “Methods”.

ROME III defines constipation as the presence of 2 or more symptoms (straining for defecation, lumpy/hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction,
manual maneuvers and < 3 bowel movements per week) at least 25% of time for > 3 months with onset at least 6 months.

Page7, line 42, please define the abbreviation "PDSS"

Thanks for the reviewer. We have added the definition in the “Methods”. Parkinson’s Disease Sleep Scale : PDSS

Page8, line 38, please define the "onset of constipation." Is it merely by the patient's recall ?

Thanks for the reviewer. We have added the definition in the “Methods”. If the patients have constipation according to ROME III questionnaire, they were asked the presence of constipation as well as the time when they had been first noticed by patients relative to onset of motor symptoms. This was subjective and retrospective. Other studies, for example, ‘The ONSET PD Study’ (Ref Pont-Sunyer C et al. 2014), have the same design. However, potential recall errors may have biased data collection. We have talked about this in ‘Limitation’.

Page8, line 55, "In regards to …" should be "With regards to …"

Thanks for the reviewer. We have changed.

Page 9, line 26, "… more longer …" is the wrong grammer

Thanks for the reviewer. We have changed.

Page 14, table 3, line 24, "Taiwan is not Taiwan, China." Be ware of political issue.

This is a scientific research and has nothing to do with political issue.
Discussion

Page 16, line 26, please explain the significance of "daily levodopa per weight" and its relation to the constipation.

Dopaminergic treatments may contribute to constipation. Our data showed that there was no difference of "daily levodopa per weight" between PD with constipation and PD without constipation. However, we found that levodopa equivalent dosage in two groups was significantly different. It might suggest that dopamine agonists have more impact on constipation than levodopa, with was consistent to some researches (Cochrane Database Syst Rev 2008;2:CD006564; Lancet Neurol 2015;14:625)

Page 16, line 41, " … prevalence of pre-motor constipation was range …" wrong grammar

Thanks for the reviewer. We have changed.

Page 16, line "41-42", "Compared with PD patients with constipation post-motor symptoms, we focus on the features of patients with pre-motor constipation, their motor symptoms presented later, the disease duration was shorter, the motor symptoms were less serious based on the lower scores of UPDRS III and H-Y stage." Please refine the sentence.

Thanks for the reviewer. We have changed.

Page 17, paragraph 1, is the difference of duration between the onset of constipation and Parkinson motor symptom attributed to genetic issue?

The association between different durations and genetic background is not clear. No related reports have been found yet.
Please discuss why PD with pre-motor constipation in your study is associated with non-tremor subtype of PD, anxiety, depression and insomnia. Is it related to different pathway of degeneration?

In our study, there was no difference in initial motor subtype between ‘constipation pre-motor’ group and ‘constipation post-motor’ group (Table 2). However, compared with PD patients without constipation, those with constipation have more non-tremor subtype and were prone to have anxiety, depression and insomnia.

Psychological disorders (anxiety, depression, ect) may lead to constipation through inhibiting the control of peripheral autonomic nervous on the colon. It could affect the autonomic nervous system, especially the parasympathetic nerve, through the cerebral cortex with results of bowel dilatation, intestinal hypomotility and diminution of gastrointestinal secretion. Our data showed that PD patients with non-tremor subtype were prone to have constipation, anxiety, depression and insomnia. This supported that PD varies dramatically in its clinical manifestations, suggesting it may be divisible into subtypes. This is useful to better understand underlying mechanisms, predict disease course, and eventually design more efficient personalized management strategies. The mechanism for subtype differences is unclear. Potential explanations include the variability in comorbid pathology (eg, synuclein in the cortex), the relative vulnerability of substantia nigra, or perhaps even the variable propensity for synuclein pathology to spread from region to region. This might be a hotspot in the field of PD non-motor symptoms in the future.

Please discuss the limitation of the study

Thanks for the reviewer. We have added the limitation in ‘Discussion’.

Our study has some limitations. This is a retrospective clinical study in which the information of chronology of constipation and motor symptoms were collected through patients’ recalls. Therefore, recall bias could not be ignored and might partially influence the accuracy of our results. In addition, the constipation in our study was confirmed by inquiring patients’ daily defecation habits, according to ROME III criteria. Our results would be more convincing if we
identified the constipation with objective markers of colonic function (Knudsen K et al, 2017). However this kind of result has never been reported. Since this is a single-center retrospective study, the results still requires to be testified by more studies including multicenter clinical studies.

Doreen McClurg (Reviewer 2): Thank you for this interesting paper. Constipation is often an overlooking symptom. My main point is the lack of explanation and detail of the survey document itself and any questions it contained. How many questions, how long did it take people to complete, were they all completed face to face, was any qualitative data collected as well? It would have been better to be more clear on these things.

Thanks for the reviewer. We have added some details in ‘Methods’.

All patients were assessed directly by movement disorders doctors face to face. The patients were asked several questions to obtain socio-demographic and clinical data. They were assessed by 10 questionnaires with Unified Parkinson’s Disease Rating Scale (UPDRS), Heohn-Yahr (H-Y) stage, Non-Motor Symptoms Questionnaire (NMSQuest), Mini-Status Examination (MMSE), Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), Parkinson’s Disease Sleep Scale (PDSS), Parkinson’s Disease Questionnaire-39 items (PDQ-39), ROME III functional constipation criteria, the Cleveland Constipation scoring System (CCS) and Patient Assessment of Constipation Quality of Life scale (PAC-QoL). It usually took 1-1.5 hours to complete. These questionnaires were widely accepted by neurologists.

Otherwise, we have improved our English language within the manuscript.