Author’s response to reviews

Title: Pisa syndrome induced by switching of a choline-esterase inhibitor treatment from donepezil to galantamine: A case report.

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Author’s response to reviews:

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Editor-in-chief of BMC neurology

Dear Darren Byrne,

Thank you for giving us an opportunity to submit again a revised draft of our manuscript entitled, “Pisa syndrome induced by switching of choline esterase inhibitor treatment from donepezil to galantamine.” which we submitted to the BMC neurology. We also really appreciate the time and effort you and each of the reviewers have dedicated to providing important opinions on our paper.

To facilitate your review of our manuscript, the following is a point-by-point response to the questions and comments delivered in your letter dated 31-March-2020.

Response to Comments from Reviewer 1.

Comment #1
The authors are suggested to include a table including all reported cases of PISA syndrome following exposure to cholineesterase inhibitors (ChEIs). This will further strengthen the hypothesis proposed by the authors.

Response to Comment #1
We really appreciate your insightful suggestion. According to your suggestion, we have added Table 1 including all past case reports, in which Pisa syndrome following initiation of ChEIs was described. In order to review the past reports, we have added six references (Ref 12-17).

Changes to Manuscript
We reviewed and summarized all case reports that described PS linked to ChEIs initiation in Table 1.

Response to Comments from Reviewer 2:

Comment #1
This is an interesting and well-presented case report adding further evidence on the possible development of PS in Alzheimer patients treated with AchEIs. The novelty of the case is represented by the fact that PS seems to be selectively provoked by a specific AchEi (galantamine) after switching from donepezil. The discussion is well-documented.

Response to Comment #1
Thank you very much for your comments and we are sincerely grateful for all your time in reviewing our manuscript.

Response to minor edits:

#1 Abstract
When explaining the hypotheses, please avoid using the term dystonia since, in most cases, PS has uncertain pathogenesis, and dystonia is only one of the hypotheses, but no clues of dystonia (such as sensory trick, overflow, nor electromyographic signs of co-contraction) have been observed so far.

Response to minor edits #1
We agree with your idea and have incorporated this suggestion throughout our paper. We have revised sentences as follows.

Changes to Manuscript
(Line 3, Pragraph 1 in Case presentation in Abstract)
Therefore, we propose two novel hypotheses to explain the development of PS, as follows; galantamine, which enhances dopamine release, can induce imbalance of dopamine levels in the striatum of patients with dementia, resulting in PS, and the weaker muscarinic effects of the drug could be one of the factors predisposing to the development of PS.

#2 Introduction.
As for the comment above, please avoid starting defining PS as a form of dystonia because this is incorrect for what we know so far. I suggest for the definition of PS to cite the paper form Doherty et al. (2011), and Tinazzi et al. (2016). On the other hand, it is fine, a few lines below, to consider and report cases of PS considered as tardive dystonia.

Response to minor edits #2
We really appreciate your insightful comments on definition of PS. We have revised a sentence in line 1 in Background accordingly and added a reference as follows.

Changes to Manuscript
(Line 1 in Background)
Pisa syndrome (PS) or pleurothotonus, is characterized by a marked lateral trunk flexion that can be reduced by passive mobilization or supine positioning [1], and was originally described by Ekbom in 1972 [2].
#3 Introduction.
I suggest rephrasing as follows: "… Disruption of the cholinergic-dopaminergic balance could result in an asymmetric axial muscle tone activation, and this is the hypothesized pathogenic mechanism underlying the development of drug-induced PS."

Response to minor edits #3
Thank you for your suggestion. We have revised the sentence accordingly.

Changes to Manuscript
(Line 8 in Background)
Disruption of the cholinergic-dopaminergic balance could result in an asymmetric axial muscle tone activation, and this is the hypothesized pathogenic mechanism underlying the development of drug-induced PS.

#4 Case presentation.
Please, give more details on how other parkinsonian signs and symptoms have changed after the removal of galantamine. Is freezing improved, for example?

Response to minor edits #4
You have raised an important question, and we have reflected this comment as follows.

Changes to Manuscript
(Line 5, Paragraph 4 in Case presentation)
After discontinuation of galantamine while continuing memantine monotherapy, the characteristic posture of PS gradually improved within 2-3 days. In accordance with improvements on posturing, her freezing of gait also disappeared so that she was able to walk without any assistance. Meanwhile, her masked face was preserved. Finally, her posturing almost thoroughly disappeared over the subsequent 14-day period (Fig. 1).

#5 Discussion
Based on recent literature data associating PS with visual-spatial function impairment (Artusi et al., 2019; Vitale et al., 2016) and the remarkable involvement of these functions in the reported patient, I suggest extending the discussion of your case.

Response to minor edits #5
We really appreciate your important suggestion, and we think this is a quite interesting perspective. We have added the paragraph, in which we demonstrated the relationships between PS and visual-spatial perception and body schema.

Changes to Manuscript
(Add paragraph 6 in Discussion and Conclusion as follows.)
In addition to switching ChEIs, the patient’s impaired visuo-spatial function might be related to PS in the presented case. According to previous reports, visuo-spatial dysfunction assessed by Benton’s judgement line orientation test was a strong and significant predictor for developing PS [33, 34]. Given the abnormal posture in PS, however, disruption in body schema, rather than visuo-spatial dysfunction, might influence the development of PS because the main atrophic area involved the bilateral parietal lobe, which is considered the neural basis for body schema [35]. Still, switching was a major cause because posturing was completely resolved after discontinuation of galantamine.
#6 Discussion
Please, rephrase the following as follows: "The Naranjo score of 5 indicates that galantamine was the probable cause of PS in our case."

Response to minor edits #6
Thank you for your suggestion. We have revised the sentence accordingly.

Changes to Manuscript
(Paragraph 7, Line 5 in Discussion and Conclusion.)
The Naranjo score of 5 indicates that galantamine was the probable cause of PS in our case [36].

Other minor edits:
Changes to Manuscript
(Line 3 in Background in Abstract)
We have rewritten line 3 in Background as follows because we used “although” twice.

Despite the fact that the precise mechanism remains unclear, cholinergic-dopaminergic imbalance has been considered as a possible pathophysiologic mechanism underlying the genesis of PS.

Once again, we thank the editor and reviewers for their feedback and look forward to your reply.

Sincerely yours,

Yu Mimura