Author’s response to reviews

Title: Pyramidal system involvement in progressive supranuclear palsy - a clinico-pathological correlation

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Author’s response to reviews:

Technical Comments:

1. Please include your declaration section before the "Reference" section.

Editor Comments:

Thank you for your submission. This is an interesting report and we would be interested in reviewing a revised manuscript addressing the concerns raised by the reviewers below. More specifically there needs to be more details in regards to the clinical chart data and the semi-quantitative rating scale developed.

Thank you for considering our manuscript. We have provided additional information to the text and table accordingly.

It is very difficult to grade clinical symptom severity retrospectively and instead reporting the presence or absence of these features along with the time duration from the onset of disease where they were noted in the record may be more informative.
- We modified our clinical approach, instead of 0-1-2 (absent – mild – severe) only 0 (absence) and 1 (presence) are now listed. This modification does not affect our statistical analysis, as only fully developed manifestation (formerly 2, updated 1) was used for statistical comparisons with the absence of the relative sign.

Table 2 is very difficult to discern semi-quantitative pathology ratings for each region, please revise for clarity.

- Table 2 was updated.

Finally, please be explicit in reporting the statistical tests planned and performed for the study in the methods and report findings appropriately according to statistical conventions in the results section.

- We modified the manuscript accordingly.

Reviewer reports:

Alexander Pantelyat (Reviewer 1):

ABSTRACT

"Background" Needs to be a complete sentence linking to the topic of PSP.

- We modified the abstract, to read: “We aimed to produce a detailed neuropathological analysis of pyramidal motor system pathology and provide its clinical pathological correlation in cases with definite progressive supranuclear palsy (PSP).”

Methods

Specify whether PSP subtyping was performed according to the 2017 MDS PSP criteria (Hoglinger et al.) or something else.

- We specified in the abstract as follows: “Based on a retrospective clinical analysis, cases were subtyped according to Movement Disorder Society criteria for clinical diagnosis of PSP as probable, possible or suggestive of PSP with Richardson’s syndrome (n = 10), PSP with predominant corticobasal syndrome (n = 3), PSP with predominant parkinsonism (n = 3), PSP with predominant speech/language disorder (n = 1), PSP with progressive gait freezing (n = 1).”

Conclusion
The phrase "and may distinguish the classic Richardson syndrome subtype from other progressive supranuclear palsy subtypes" should be edited to reflect that the distinction is pathological (eg, "may distinguish on autopsy"), since the RESULTS section states "however, there was no significant correlation between pyramid system tau pathology and related motor clinical symptoms."

- Thank you for this comment, we modified the text, now it reads: “Tau pathology in the spinal cord and pyramid motor system structures is very common in progressive supranuclear palsy and may neuropathologically supplement the distinction between the classic Richardson syndrome from other progressive supranuclear palsy subtypes.”

Page 4, Line 15--Specify whether you are referring to median survival from diagnosis or from symptom onset.

- We specified the statement to read: “median survival from onset to death of approximately 8 years” and added a relevant reference (Chiu et al., JNNP 2011).

Page 6, Lines 25-33--Specify whether subtype assignment was according to the 2017 MDS PSP criteria. If so, please specify level of diagnostic certainty ("probable", "possible", or "suggestive of")

- Information about disease duration from the onset to death is available for all patients and now specified for each case in the supplement file, as well as precision about the level of diagnostic certainty can also be found there.

Page 9, Lines 1 and 33--these are inconsistent as the authors first mention excluding 3 patients from analysis and then mention 6.

- Thank you for this remark, we fully agree. We modified the manuscript (now it reads “Brain samples from 18 diseased patients (13 males and 5 females) with definite PSP and without neurodegenerative comorbidity nor serious cerebrovascular pathology were considered for the study.” Both the supplement file and table were changed accordingly (now only clinical data concerning the enrolled 18 patients are given).

Page 10, Line 17--specify what is meant by "clinical scores"

- We simplified our semiquantitative scoring system: three categories (bulbar signs, pseudobulbar signs, spasticity signs – all specified in the text) and two options: absent or present.

Page 13, Line 48--This would be a good place to add comments about disease duration for the patients examined, as well as the gap between last clinical assessment and autopsy. These would have a direct bearing on the analysis, discussion and conclusions.

- In our retrospective assessment, we were able to determine the time span between disease onset and death and this information is available for each patient in the supplementary file. Data concerning disease progression in terms of different symptomatology progression were very
inconsistent, we were able to identify retrospectively key features in most patients (oculomotor palsy, falls, gait disorder, parkinsonism, dementia, bulbar and pseudobulbar signs), but it was rather difficult, in some cases, to retrace the evolution timeline. We also decided (as mentioned before and reflecting both Reviewers’ and Editor’s suggestions) that the assessment of presumed pyramidal tract involvement should be simplified (into a binary assessment, i.e., absent vs. present).

Page 15, line 46--Edit "Since PSP-RS patients have a more rapid disease progression and more severe disability than non-RS forms, and since individual prognostic markers for PSP patients are still missing, the detection of pyramidal symptoms in PSP could have prognostic importance." to "Since PSP-RS patients frequently have a more rapid disease progression and more severe disability than non-RS forms, and since individual prognostic markers for PSP patients are still lacking, the detection of pyramidal symptoms in PSP may have prognostic importance, although our study was not designed to address this issue."

- We modified the conclusion accordingly (with slightly different wording).

Table 1--Specify whether diagnoses were determined using the 2017 MDS PSP criteria. Add a column specifying time from last available clinical observation to autopsy.

- We added precision about the respective PSP subtypes according to the 2017 MDS PSP criteria and disease duration from onset to death into table 1, due to inconsistent retrospective data, the time from last clinical observation to autopsy was not possible to specify for all cases.

Gesine Respondek (Reviewer 2):

In their study "Pyramidal system involvement in progressive supranuclear palsy - a clinico-pathological correlation", Zuzana Stejskalova and colleagues analysed AT-8 tau pathology in the pyramidal system and retrospective clinical data in 25 autopsy-confirmed patients with PSP with different clinical presentations. They found more tau pathology in the pyramidal system in PSP patients with Richardson's Syndrome. The severity of clinical features associated with the pyramidal system did not correlate with the severity of pyramidal tract pathology and did not differ across different PSP phenotypes.

Involvement of the pyramidal system in PSP has been reported earlier. A novel aspect of this study is the comparison of different PSP phenotypes. While this is important, I have several concerns regarding methodology and interpretations of results in this paper:

Case selection:

It needs to be clarified how many patients contributed to the clinical and pathological findings. In my understanding, only 19 patients are included into final analysis. In that case, it is redundant to
talk about 25 patients or it needs to be clarified what kind of additional information is taken out of these 6 excluded cases.

- Thank you for this remark, we fully agree. We modified the manuscript (now it reads “Brain samples from 18 diseased patients (13 males and 5 females) with definite PSP and without neurodegenerative comorbidity nor serious cerebrovascular pathology were considered for the study.” Both the supplement file and table were changed accordingly (now only clinical data concerning the enrolled 18 patients are given).

Clinical data:

How detailed was the retrospective clinical data and at what stage of the disease was it collected? It is conceivable that clinical information was not available shortly before death in many cases, which could explain the lack of correlation between pathological findings. This should be discussed.

- This is also a point needing clarification, thank you. In our retrospective assessment, we were able to determine the time span between disease onset and death and this information is available for each patient in the supplementary file. Data concerning disease progression in terms of different symptomatology progression are very inconsistent, we were able to identify retrospectively key features in most patients (oculomotor palsy, falls, gait disorder, parkinsonism, dementia, bulbar and pseudobulbar signs), but it was rather difficult, in some cases, to retrace the evolution timeline. We also modified Table 1 and Supplementary Table accordingly.

The presented new semiquantitative scoring system requires fairly detailed clinical data. Was it really possible to retrospectively extract spastic dysarthria versus bulbar dysarthria, spasticity versus rigor, decreased gag reflex and soft palate palsy?

- We decided (as mentioned before and reflecting both Reviewers’ and Editor’s suggestions) that the assessment of presumed pyramidal tract involvement should be simplified (into a binary assessment, i.e., absent vs. present).

The initial patients’ clinical records were generally very detailed, so pyramidal tract signs (and characteristics of dysarthria manifestation, gag reflex, motility of the soft palate and uvula) were either clearly noted as present or clearly noted as absent. In contrast, follow-up data became far most heterogeneous.

Authors should discuss that the lack of validation of their scoring system (and lack of detailed clinical data?) might contribute to the failure to find any correlation between pathological and clinical pyramidal tract impairment.

- Due to the retrospective character of our study, we are unable to provide a more categorical conclusion. In concordance with a suggestion of Reviewer 1, we modified the conclusion as follows: “Since PSP-RS patients frequently have faster disease progression and greater disability
than non-RS forms, and since individual prognostic markers for PSP patients are still lacking, the detection of pyramidal symptoms in PSP may have prognostic importance, although our study was not designed to address this issue."

Pathological data:

Pathological findings on neuronal loss in the pyramidal tract regions in this cohort should be displayed in results and discussed.

- Thank you for the comment on this important issue. While analyzing cases, we semiquantitatively assessed this parameter and no significant neuronal loss was observed. Nevertheless, we did not include this finding in the manuscript due to the fact, that the samples were obtained primarily for diagnostic purposes during routine brain dissection, and therefore exact stereological equivalence among examined areas could not be both maintained and relied upon, which, we believe, is the major reason for low reliability of obtained (semi)quantitative data regarding neuronal count.

Statistics:

Besides the mean and median of RS and non-RS of total neuropathological scores, SD or range should be given.

- According to reviewer’s suggestion, the range of total neuropathological scores has been added as min and max values: “RS (median = 36, mean = 34.8, min = 25, max = 43) and non-RS (median = 22, mean = 23.4, min = 6, max = 45)”.

Multiple comparison correction should be applied.

- In accordance with the main hypothesis, the WMW test of total neuropathological scores has been applied one time, i.e., without the False Discovery Rate (FDR) correction. Following detailed testing of local neuropathological scores in selected domains should be corrected by FDR due to multiple comparisons. But in the absence of the FDR correction, there were only nonsignificant score differences. Therefore, the application of adstringent FDR correction leads to the same results.

Kevin Bieniek (Reviewer 3)

"Pyramidal system involvement in progressive supranuclear palsy - a clinicopathological correlation" by Stejskalova et al. is a descriptive study regarding the presence of motor system pathology and pyramidal signs in autopsy-confirmed PSP cases with different clinical subtypes. The authors employ semi-quantitative scoring systems to assess bulbar signs, pseudobulbar
signs, and spasticity as well as tau-immunoreactive neurofibrillary tangles, coiled bodies, tufted astrocytes, and neuropil threads in various neuroanatomical regions. The cohort is well characterized (predominantly in the Supplemental Material) and the manuscript is well-written.

My biggest concern is that while a statistical significance was detected between total neuropathological score in motor regions of PSP-Richardson versus PSP-non-Richardson cases, this finding does not appear to translate to a meaningful finding of clinical or pathological relevance. Specifically, the authors state "there were no statistically significant differences in any individual domain between PSP-RS and non-RS patients" (pathology) and "we found no significant difference between the RS and non-RS subgroups relative to their clinical scores and their sum".

- Thank you for addressing the contradiction in the text. The right formulation is: "we found no significant difference between the RS and non-RS subgroups relative to their local clinical scores"

Greater clarity is needed regarding what the "individual domain" represents - does the total score summate all types of tau immunoreative pathologies (NFTs, TAs, CBs)?

- We focused on specific brain and spinal cord areas (domains) defined neuropathologically (motor cortex, capsula interna, crura cerebri, pons, anterior spinal horns, posterior spinal horns, lateral corticospinal tract, posterior fascicles). Semiquantitative assessments of the degree of neuropathological changes (absent, mild, moderate, severe) are detailed in Table 2.

Are there differences in total scores of specific pathological lesions?

- There were not differences in total scores, as can be seen in the modified Table 2, we hope, this table formatting is easier to read.

Does a domain represent all pathologies in a single anatomical regions?

- In every domain we observed almost all counted pathologies, we scored this semiquantitatively as mentioned in the table, which was changed for better orientation. We deleted supplementary data not entered into the statistical analysis as well as results from patients excluded from the study.

Some additional comments regarding the manuscript are as follows:

Sections 2.5 (Statistical methods) and 3 (Results) appear to contradict each other. Section 2.5 states neuropathological data were available for all 25 study cases and clinical data was "incomplete in 3 cases and these patients were eliminated from the statistical analysis" (together suggesting a total of 3 cases excluded). The beginning of Section 3 states "six patients were excluded from statistical analysis because of incomplete clinical or neuropathological data".
- Thank you for this remark, we fully agree. We modified the manuscript (now it reads “Brain samples from 18 diseased patients (13 males and 5 females) with definite PSP and without neurodegenerative comorbidity nor serious cerebrovascular pathology were considered for the study.” Both the supplement file and table were changed accordingly (now only clinical data concerning the enrolled 18 patients are given).

Table 2 is quite difficult to read. The table would benefit from either inverting the table to a horizontal format or using alternate shading of consecutive rows to delineate the different semi-quantitative scores.

- We changed the table, different shades of gray demonstrate density of neuropathy changes, clinical symptomatology was changed to positive (+) or negative (−). Moreover, we shortened the table, neuropathological areas, not crucial for evaluation, were removed. We hope that Table 2, in its new format, will be easier to read.