Author's response to reviews

Title: Proteinase-activated receptor 2 and disease biomarkers in cerebrospinal fluid in cases with autopsy-confirmed prion diseases and other neurodegenerative diseases.

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Author's response to reviews: see over
Dear Editors,

Please find our responses to the reviewer’s remarks below. The comments and suggestions of the reviewers have been incorporated into the current (attached) revision of our manuscript entitled “Proteinase-activated receptor 2 and disease biomarkers in cerebrospinal fluid in cases with autopsy-confirmed prion diseases and other neurodegenerative diseases.”

We would like to thank both reviewers for their stimulating and constructive remarks and comments.

Based on comments, the text has been edited regarding language and formal content. We also submitted the edited manuscript for additional language proofreading by an American editor who specializes in scientific editing.

Please note that we have also expanded the correlation analysis with respective parts now appearing in the Results and Discussion sections of the manuscript (please see further details below).

Yours sincerely,

Zdenek Rohan, Magdalena Smetakova, Jaromir Kukal, Robert Rusina, Radoslav Matej
Title: Proteinase-activated receptor 2 and disease biomarkers in cerebrospinal fluid in cases with autopsy-confirmed prion diseases and other neurodegenerative diseases.

Reviewer 1

Abstract

The second sentence of the background section (line 32-34) is not very clear (cerebrospinal fluid is not a marker of neuronal damage, maybe cerebrospinal fluid tau is) and should be reviewed for English (e.g. neurodegenerations could be changed in neurodegenerative disorders).

In the objective section of the abstract (line 35) the acronym CSF should be reported at the first citation (line 33) and not at line 35.

- page 3, lines 32–53 - edited accordingly

Please use the same terms across the manuscript (phospho-tau at line 36 and phospho tau at line 39, as well as total-tau and total tau). Review punctuation and the use of “and”.

Review syntax and English at line 44-46.

Review English at line 49 (high total-tau CSF levels protein positivity). Correctly identify the acronym CJD in this line.

- Use of T-tau, P-tau and Aβ unified throughout the manuscript; language edited accordingly

Main text:

At line 61 the authors could clarify the mechanisms underlying PAR activation (e.g. activated by proteolytic cleavage of the extracellular amino terminus).

- page 5, lines 60–63 + now includes a more precise mechanism of PAR activation, as suggested

When identifying acronyms or abbreviations the authors should keep the same term throughout the whole text (e.g. P-tau181p at line 72 and then p-tau at line 78; this goes also with A#(1–42) and A#.

- Abbreviations and acronyms unified throughout the manuscript

Review line 84 for English: (e.g. were assessed clinically and neuropsychologically, underwent....)

- language edited accordingly

Line 89: “see Table 2”: are the authors referring to the table in the supplementary material? There is no Table 2 in the manuscript, please clarify.
We thank the Reviewer for noting this typo, Table 2 renamed as “Supplemental table”

Table 1: third row, fourth column: “2-84” this is a range, not the median, please correct.

Line 111: correct abbreviations “B-amy”, etc.

- Table 1 reformatted according to comments of both Reviewer 1 and Reviewer 2

When reporting p-values, perhaps it is best to write only 3 digits after the comma (e.g., p=0.005, or p<0.001 for cases with very low p-value and do not use exponentials)

- P-values reformatted as suggested by the Reviewer

Reviewer 2

1. In abstract, Results: “We did not find any significant difference between levels of PAR-2 and other biomarkers”. This sentence may point that PAR is similar to tau biomarker - which is not the case. The authors may mean that no difference was detected between CJD and non-CJD.

- We thank the reviewer for noting this imprecision, we edited text accordingly (page 3, line 43)

2. The table in not clear (SD values are usually not presented this way). Significant p values should be presented.

- Table 1 reformatted according to comments of both Reviewer 1 and Reviewer 2
- Even though some results are statistically significant, the authors would like to keep Table 1 as clear as possible. Important p-values are mentioned throughout the text.

3. Comparing CJD to non-CJD is not so relevant for amyloid and p-tau levels (while it may make sense for t-tau only). Dividing the non-CJD cases to subgroups of AD etc. (although small groups) is needed. Indeed the raw data is presented in supplement but should be summarized in results.

- We added non-CJD disease groups to Table 1

4. Actually, the main conclusion is that PAR cannot serve as marker in the order to tau, where very high and significant difference exists between CJD and non-CJD.
Thank you for this comment, we edited the Discussion section on page 9, lines 156–157.

5. That the tau has higher specificity than 14-3-3 has been also published by Miner et al. J Neurol 2011

- We found this remark very useful, we added this interesting work focusing on genetic forms – Meiner et al. J Neurol (#11) reference added. In addition, we added the following references: Ladogana et al. J Neurol (#12) and Sanchez-Juan, Neurology (#13)

Additional changes made by the authors:

Page 6, lines 97–99, 101–102 – reagent specifications added
Page 7, lines 117–120 – correlation testing methodology added
Pages 8–9, lines 143–151 – correlation results added
Page 9, lines 161–166 – correlation results discussed
Additional minor language corrections (typos and syntax) made throughout the text.