LETTER TO THE EDITOR

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Response to the letter "The effect of Alzheimer's disease comorbidity in tap test response in idiopathic normal pressure hydrocephalus?" from Dr. Onder *et al.*

We thank Dr. Onder and colleagues for their comment on our research investigating the association between cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) and tap test response in patients with idiopathic normal pressure hydrocephalus (iNPH; Kanemoto *et al.*, 2021). We agree with the authors on the limitation of CSF biomarkers in iNPH. This is the same point we mentioned as the first limitation in our original paper, and we had also concluded that the results of the paper need to be carefully interpreted in light of this limitation.

The authors of the letter suggest that the clinical and neuroimaging signs of AD should be used to support AD comorbidity in addition to CSF biomarkers. It was reported that orientation and memory were more impaired in AD than in iNPH (Ogino *et al.*, 2006). Some neuroimaging studies also have reported useful indicators to distinguish iNPH from AD, ventricular dilatations with dilated sylvian fissures and tight sulci in the medial parietal lobes, enhanced perfusion in areas surrounding the cingulate gyrus, and so on (Nakajima *et al.*, 2021). Therefore, the score of the Rivermead Behavioral Memory Test (RBMT) and magnetic resonance image collected in our study may be used as an index to assess AD-like characteristics. However, because these features are the characteristics of AD compared to iNPH, we might not be able to simply use them to examine the differences between iNPH patients with and without the comorbidity of AD. Some previous studies investigating the differences of the effect of shunt surgery on iNPH patients with and without AD using autopsy or amyloid imaging did not examine the differences in detail cognitive profiles or neuroimaging before shunt surgery. One previous study showed that trends toward larger volumes of hippocampus were observed in NPH patients without AD pathologic findings than those with, although not statistically significant (Savolainen *et al.*, 2000). However, iNPH shows severe morphological changes in brain, making it technically difficult to verify brain volume or perfusion using statistical methods such as Statistical Parametric Mapping. There are many challenges in assessing AD-like features. Evaluation of biopsy specimens and amyloid imaging may be preferable to confirm AD comorbidity in iNPH more reliable than CSF biomarkers. As the authors pointed out, lack of these data is the main limitation in our study.

The second point the authors mentioned about the problem of the method to evaluate the results of tap test is consistent with the discussion we described in the fifth paragraph of Discussion in our original paper. We also agree with the speculation that more detailed neuropsychological tests for memory and frontal lobe function should be used to evaluate the response to tap test in iNPH patients with suspicion of AD pathology.

Thirdly, the authors asked for the statistical analysis of the difference in clinical symptoms at baseline between the groups. We described it in original Table 1, and there were no statistically significant differences in any clinical variables between the groups at baseline.

We consider that the authors' suggestions are reasonable and are consistent with our conclusions. The results of CSF biomarkers related to AD in iNPH should be assessed with caution. It has been reported that iNPH patients with suspected AD comorbidity may also show improvement with tapping and shunting in some studies. In addition, our present study showed that a part of cognitive battery after tapping and total condition after shunting were improved in some iNPH patients with negative result in the tap test, which indicated false-negative in the current method. The latest guideline also pointed out the low sensitivity of tap test in iNPH (Nakajima *et al.*, 2021). Further research on modified methods is needed to improve the accuracy of tap test for iNPH.

Conflict of interest

None.

Author contributions

H.K. wrote the initial draft of the manuscript. E.M. and M.I. contributed to the revision of the draft.

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