Author’s response to reviews

Title: Prevalence of and risk factors for enlarged perivascular spaces in adult patients with moyamoya disease

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Professor Andreas Charidimou,
Editor, BMC Neurology

Dear Sir,

Thank you for your kind letter regarding our recently submitted manuscript. I have responded to the reviewers’ concerns on a point-by-point basis, and the responses are presented below. I understand that final acceptance depends on satisfactory resolution of these issues.

Editor

Please comment why other lesions were not assessed, e.g. microbleeds, lacunes etc.
Response:

Thank you for your comment. To avoid confusion regarding the statistical analysis, we selected the items that are considered to be related to high EPVS from the results of Table 3. In the revised version, this was mentioned in the Discussion section as follows:

“In terms of lacunar stroke and microbleeds, their prevalence values were higher in the high EPVS grade group than in the low EPVS grade group though it was not significant. From the viewpoint of small vessel disease, high EPVS is associated with other morphological features, such as white matter hyperintensities and lacunar stroke[8, 10, 42]. In this study, these items could not be included in the multivariate analysis because their p values were less than 0.10 in the Mann-Whitney U tests and Chi-squared test. Although their sample size and prevalence were small in this study, their interaction might be apparent with a greater number of cases.”

Tackeun Kim, M.D. (Reviewer 2)

1) Although the authors have revised the manuscript well, fundamental question is not solved yet. Through the manuscript, the authors concluded that adult MMD patients exhibited more EPVS than control group. But they reported higher prevalence of HTN among MMD group. Considering the relationship between EPVS and HTN, hypertension could be a source of EPVS in MMD. With the data on manuscript, the ratio of HTN among lower EPVS MMD (12/35) was similar with the ratio among control group (9/41). The p-value by Fisher's exact test is 0.461. If authors wanted to conclude that EPVS could be induced by MMD, the prevalence of HTN should be matched between MMD and control group. If it is not possible, multivariate analysis between MMD and control group should be performed by stratifying HTN variable, at least.

Response:

Thank you for your insightful comment. The prevalence of hypertension could not be matched between the moyamoya disease group and the control group. Therefore, multivariate analysis was performed, and the selection bias was discussed as follows in the Discussion section:

“On the other hand, the prevalence of hypertension in the moyamoya disease group was significantly higher than that in the control group, as shown in Table 1. Moyamoya disease is often accompanied by hypertension[30, 31], and a recent study suggested that a polymorphism of RNF213 is also associated with systolic blood pressure[32]. The prevalence of hypertension is higher than that in the age-sex matched control group. Although there is a possibility that hypertension might have a statistical influence in the comparison of clinical characteristics of high EPVS grade, hypertension was not selected as a confounding factor in the multivariate
analysis comparing the moyamoya disease group and the control group. Therefore, the selection bias will not be high for evaluating high EPVS.”

2) Second, IQR had better to be presented as (1st quartile - 3rd quartile) to provide more readable distribution status.

Response:

In accordance with the reviewer’s comment, the data were expressed as median (1st quartile-3rd quartile) values in the revised version.

We appreciate the reviewers’ thorough assessment of our paper. We would be grateful for a third review of our manuscript for possible publication in BMC Neurology.

With best regards,

Takeshi Mikami, M.D.