Author's response to reviews

Title: Relation between aphasia and arcuate fasciculus in chronic stroke patients

Authors:

Hyung Jun Tak (takhjji@naver.com)
Sung Ho Jang (strokerehab@hanmail.net)

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Author's response to reviews: see over
Relation between aphasia and arcuate fasciculus in chronic stroke patients

Abstract-Method: Twenty five consecutive right-handed stroke patients with aphasia following lesions in the left hemisphere were recruited for this study. The aphasia quotient (AQ) of Korean-Western Aphasia Battery was used for assessment of language function. We measured values of fractional anisotropy (FA), apparent diffusion coefficient (ADC), voxel number of the left AF. We classified patients into three groups: type A - the left AF was not reconstructed, type B - the left AF was discontinued between Wernicke’s and Broca’s areas, and type C – the left AF was preserved around the stroke lesion.

Abstract- Results: Moderate positive correlation was observed between AQ and voxel
number of the left AF ($r=0.471$, $p<0.05$). However, no correlation was observed between AQ and FA ($r=0.275$, $p>0.05$) and ADC values ($r=-0.286$, $p>0.05$). Significant differences in AQ scores were observed between the three types ($p<0.05$); the AQ score of type C was higher than those of type A and B, and that of type B was also higher than that of type A ($p<0.05$).

**Abstract- Conclusion:** According to our findings, the remaining volume of the left AF, irrespective of directionality and diffusivity, showed moderate positive correlation with language function in chronic stroke patients with aphasia. Discontinuation or non-construction of the left AF was also an important factor for language function.

**Result-**

Moderate positive correlation was observed between AQ and voxel number of the left AF ($r=0.471$, $p<0.05$) [31]. However, no correlation was observed between AQ, and FA ($r=0.275$, $p>0.05$) and ADC values ($r=-0.286$, $p>0.05$).

**Discussion**

In this study, using DTT, we analyzed the status of the left AF in chronic stroke patients with aphasia and investigated relations between AQ and DTT findings of the left AF. Our results can be summarized as follows: 1) AQ showed moderate positive correlation with voxel number of the left AF. However, it did not show correlation with FA and ADC values of the left AF.

**Conclusions**

In conclusion, according to our findings, the remaining volume of the left AF, irrespective of directionality and diffusivity, showed moderate positive correlation with language function in chronic stroke patients with aphasia.
Point3: Although the AQ for type A is better than type B and type B is correspondingly better than type C, this may not be easily attributable to the AF. Type A has a much large volume of infarct than type B and type C, on the scan provided it appears that it involve the wenickes area as well. Other areas that are affected by the stroke could similarly account for this difference in AQ. While I understand it is difficult to control for this, similar stroke types with similar affected areas leaving only the AF different would be ideal.

Answer: Thank you for your precise comment. We estimated the stroke lesion volume as follows. In addition, we described this is one of limitations of this study in the section of conclusion as follows.

Method

Measurement of volume of stroke lesion

Volume of stroke lesion was measured on T2-weighted MRI images using a picture-archived communication system (PACS, Marotech, Korea). We measured maximum width (X), length (Y), and height (Z) of the lesion at the level where stroke lesion could be clearly observed. Lesion volume was calculated according to the formula [30]:

\[
\text{Lesion volume (mV)} = \frac{4}{3} \times \frac{1}{16} \times \pi \times X(\text{cm}) \times Y(\text{cm}) \times Z(\text{cm}).
\]

Statistical analysis

Statistical Package for the Social Sciences for windows (SPSS version 12.0K, SPSS Korea) was used in performance of all statistical analyses. The Mann-Whitney test was performed for comparison of significant differences of AQ, age, volume of stroke lesion(mV), DTI evaluation time post onset (days), and K-WAB evaluation time post onset (days) between the three types of the left AF.
Results

Demographic and DTT findings are summarized in Table 1. Twenty-five patients were classified into three groups according to the DTT type for the AF. Six patients belonged to the type A group (four males; mean age 49.3 ± 7.8 years; range 41 to 63 years), eleven patients to the type B group (six males; mean age 49.6±9.0 years; range 37 to 66 years), and eight patients (four males; mean age 38.6±14.5 years; range 20 to 63 years) to the type C group. No difference in distribution of age, DTI scanning time from onset, and K-WAB evaluation time from onset was observed between the three AF types ($p>0.05$). However, lesion volume of the type A group was greater than those of type B and C groups ($p<0.05$) although there was no difference between the type B and C groups ($p>0.05$).

Conclusions

One of the limitations of this study was the small number of subjects. Because this study was conducted retrospectively, we could not conduct a detailed evaluation of the language function of patients. In addition, we did not control the education level of patients and the volume of stroke lesion volume which can affect the language function. The fact that we did not analysis the other neural tracts which are involved in language function is another limitation of this study[35]. Therefore, further prospective studies to overcome these limitations should be encouraged.

Point 4: also without a preceeding MRI, how do the authors know that there are no previous infarcts and that the patients do not have any asymptomatic strokes. The educational level of the patients are not controlled as well, neither is the infarcted areas excluding the AF. Basically the patients may not start from the same baseline state.
Answer: As for previous stroke history, we already confirmed using the brain MRI at stroke onset, therefore, we revised the inclusion criteria as follows. As for the education level, we totally agree with your opinion and we described this is one of limitations of this study in the section of conclusion as follows.

**Subjects**

Twenty five consecutive right-handed patients (mean age 46.0 ± 11.6 years) were recruited according to following inclusion criteria: (1) first-ever stroke, (2) age range: 20~69 years, (3) stroke lesion was located in the left hemisphere, (4) aphasia: aphasia quotient (AQ) scores on Korean-Western Aphasia Battery (K-WAB) below 92.8, (5) DTI scanning and K-WAB were performed after three months from stroke onset, (6) no history of stroke, head trauma, or psychiatric disorder, and (7) no previous stroke lesion on the brain MRI which was taken at stroke onset [24]. This study was performed retrospectively and the study protocol was approved by the Institutional Review Board of the Yeungnam university hospital.

**Conclusions**

One of the limitations of this study was the small number of subjects. Because this study was conducted retrospectively, we could not conduct a detailed evaluation of the language function of patients. In addition, we did not control the education level of patients and the volume of stroke lesion volume which can affect the language function. The fact that we did not analysis the other neural tracts which are involved in language function is an another limitation of this study[35]. Therefore, further prospective studies to overcome these limitations should be encouraged.

Point5: Needs some language corrections before being published.

Answer: Before first submission, we had already corrected errors by a native grammatical
specialist in a scientific editing service company and this time, we corrected errors through the whole manuscript.
Reviewer #2: Prakash paliwal

Following are major compulsory revisions needed.

Point 1. In discussion author has tried to explain why FA value of the left AF does not correlate with language function but no explanation has been given for negative correlation for ADC values of left AF with language function.

Answer: Thank you for your precise comment. We revised the discussion as follows.

**Discussion**

In this study, using DTT, we analyzed the status of the left AF in chronic stroke patients with aphasia and investigated relations between AQ and DTT findings of the left AF. Our results can be summarized as follows: 1) AQ showed moderate positive correlation with voxel number of the left AF. However, it did not show correlation with FA and ADC values of the left AF. 2) AQ differed according to the discontinuation or non-construction of the left AF; specifically, poorer AQ scores were observed for patients who showed discontinuation of integrity or non-construction of the left AF on DTT, compared with patients who did not show those findings. FA value represents the degree of directionality of microstructures (e.g., axons, myelin, and microtubules), and ADC value indicates the magnitude of water diffusion [14,32]. The opposite correlation of FA ($r=0.275$) and ADC ($r=-0.286$) with AQ appear to be attributed to these characteristics of FA and ADC values [14,32].

Point 2. Additional advantage of doing Korean MMSE over Korean-Western aphasia battery is not clear and also it is not clear whether results of Korean MMSE were confounded by speech difficulty.
Answer: We totally agree with your comment. So, we removed the descriptions about the MMSE through the whole manuscript.

Evaluation of language function

The AQ of K-WAB was conducted for assessment of language dysfunction at a chronic stage of stroke (mean 229.2 ± 159.4 days after onset). Reliability and validity of K-WAB have been well-established [24-25].

Statistical analysis

Statistical Package for the Social Sciences for windows (SPSS version 12.0K, SPSS Korea) was used in performance of all statistical analyses. The Mann-Whitney test was performed for comparison of significant differences of AQ, age, volume of stroke lesion(mV), DTI evaluation time post onset (days), and K-WAB evaluation time post onset (days) between the three types of the left AF.

Result

Conclusions

One of the limitations of this study was the small number of subjects. Because this study was conducted retrospectively, we could not conduct a detailed evaluation of the language function of patients. In addition, we did not control the education level of patients and the volume of stroke lesion volume which can affect the language function. The fact that we did not analysis the other neural tracts which are involved in language function is another limitation of this study[35]. Therefore, further prospective studies to overcome these limitations should be encouraged.
Point 3. in Type A pattern as shown in figure on MRI patient is having a large Left MCA territory stroke with involvement of even Broca's and Wernicke's areas so low score on Aphasia quotient is expected and may be confounded by other areas involvement. This confounding effect has not been discussed and explained in this paper.

Answer: Thank you for your precise comment. We estimated the stroke lesion volume as follows. In addition, we described this is one of limitations of this study in the section of conclusion as follows.

Method

Measurement of volume of stroke lesion

Volume of stroke lesion was measured on T2-weighted MRI images using a picture-archived communication system (PACS, Marotech, Korea). We measured maximum width (X), length (Y), and height (Z) of the lesion at the level where stroke lesion could be clearly observed. Lesion volume was calculated according to the formula [30]:

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Conclusions

One of the limitations of this study was the small number of subjects. Because this study was conducted retrospectively, we could not conduct a detailed evaluation of the language function of patients. In addition, we did not control the education level of patients and the volume of stroke lesion volume which can affect the language function. The fact that we did not analysis the other neural tracts which are involved in language function is an another limitation of this study[35]. Therefore, further prospective studies to overcome these limitations should be encouraged.

Following minor essential revisions are needed.

Point 1. In type A pattern for left AF on DTT authors have not analysed DTT parameters reason for which should be make clear in discussion for clarity.

Answer: We described about type A in the discussion as follows.

Discussion
On the other hand, discontinuation or non-construction of the left AF was an important factor for language function in these patients. Non-reconstruction of the left AF in the type A group appears to indicate severe degeneration of the left AF following severe injury of the left AF at stroke onset.

Point 2. There are language errors and mismatch of results in Text and table 1. i.e.

a. In table 1 in type A total 6 patients with male: female 4:2 but in text in results section line 3 it is mentioned as 3 males in that group. Also in table 1 in type C total 8 Patients but ratio showing 5:5 which should be corrected to 4:4 as per text.

Answer: We corrected the errors as follows.

Result

Demographic and DTT findings are summarized in Table 1. Twenty-five patients were classified into three groups according to the DTT type for the AF. Six patients belonged to the type A group (four males; mean age 49.3 ± 7.8 years; range 41 to 63 years), eleven patients to the type B group (six males; mean age 49.6±9.0 years; range 37 to 66 years), and eight patients (four males; mean age 38.6±14.5 years; range 20 to 63 years) to the type C group.

Table 1. Demographic and diffusion tensor tractography data for the left arcuate fasciculus

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Diffuse tensor tractography type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Patient number ( male : female )</td>
<td>25(14:11)</td>
<td>6(4:2)</td>
</tr>
<tr>
<td>Age</td>
<td>46.0(11.6)</td>
<td>49.3(7.8)</td>
</tr>
<tr>
<td>Days to diffusion tensor imaging</td>
<td>181.5(75.3)</td>
<td>156.3(75.0)</td>
</tr>
<tr>
<td></td>
<td>Days to Korean-western aphasia battery</td>
<td>Volume of stroke lesion (mV)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>229.2(159.4)</td>
<td>24.8(23.7)</td>
</tr>
<tr>
<td></td>
<td>181.7(103.7)</td>
<td>58.8(25.4)</td>
</tr>
<tr>
<td></td>
<td>192.5(67.8)</td>
<td>15.0(7.8)</td>
</tr>
<tr>
<td></td>
<td>315.3(245.7)</td>
<td>12.8(8.8)</td>
</tr>
</tbody>
</table>

Values indicate mean (±standard deviation)

b. In discussion section second para line 5 "the next year" need to be corrected

Answer: We corrected as follows.

**Discussion**

Following introduction of DTI, several studies reported on the relationship of AF finding on DTI and language function in stroke patients with aphasia [15,16,18,19,23]. In 2008, Breier et al reported FA values on DTT of the left AF and superior longitudinal fasciculus scanned at chronic stage (1-72 months), showed correlation with repeatability of language in 20 stroke patients with aphasia [15]. In 2009, Hosomi et al reported on comparison of the asymmetry of FA value and fiber number between the right and left AF on DTT taken within two days from onset in 13 patients with left middle cerebral artery infarcts.

Point3: Needs some language corrections before being published.

Answer: Before first submission, we had already corrected errors by a native grammatical specialist in a scientific editing service company and this time, we corrected errors through
the whole manuscript.