White Matter Abnormalities in Traumatic Subarachnoid Hemorrhage: A Tract-Based Spatial Statistics Study

Background: The pathophysiology of traumatic subarachnoid hemorrhage and brain injury has not been fully elucidated. In this study, we examined abnormalities of white matter in isolated traumatic subarachnoid hemorrhage patients by applying tract-based spatial statistics.

Material/Methods: For this study, 10 isolated traumatic subarachnoid hemorrhage patients and 10 age- and sex-matched healthy control subjects were recruited. Fractional anisotropy data voxel-wise statistical analyses were conducted through the tract-based spatial statistics as implemented in the FMRIB Software Library. Depending on the intersection between the fractional anisotropy skeleton and the probabilistic white matter atlases of Johns Hopkins University, we calculated mean fractional anisotropy values within the entire tract skeleton and 48 regions of interest.

Results: The fractional anisotropy values for 19 of 48 regions of interest showed significant divergences (P<0.05) between the patient group and control group. The regions showing significant differences included the corpus callosum and its adjacent neural structures, the brainstem and its adjacent neural structures, and the subcortical white matter that passes the long neural tract.

Conclusions: The results demonstrated abnormalities of white matter in traumatic subarachnoid hemorrhage patients, and the abnormality locations are compatible with areas that are vulnerable to diffuse axonal injury. Based on these results, traumatic subarachnoid hemorrhage patients also exhibit diffuse axonal injuries; thus, traumatic subarachnoid hemorrhage could be an indicator of the presence of severe brain injuries associated with acute or excessive mechanical forces.

Keywords: Anisotropy • Diffusion Tensor Imaging • Spatial Analysis • Subarachnoid Hemorrhage, Traumatic

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Background

Subarachnoid hemorrhage (SAH) results in an accumulation of blood in the subarachnoid space and is mainly a sequela of head trauma [1]. Traumatic SAH occurs in 26-53% of traumatic brain injuries patients [2]. Previous studies have reported that traumatic SAH patients, either alone or with other brain injuries, have a poor outcome [3-7]. As a result, it has been argued that traumatic SAH can be an indicator of the presence of severe traumatic brain injuries. Among SAH-related secondary brain damages, post-traumatic vasospasm, hypothalamic-pituitary axis dysfunction, and hydrocephalus have been suggested as causes of the poor outcome in SAH patients [8-14]. However, the pathophysiology of traumatic SAH for brain injury has not been fully elucidated. Many studies have reported that traumatic brain injuries in most patients are accompanied by focal axonal injury or diffuse axonal injury (DAI) [15-23]. As SAH may be accompanied by axonal injuries, we hypothesized that traumatic SAH would be accompanied by traumatic axonal injuries.

Diffusion tensor imaging (DTI) allows the assessment of the white matter integrity because of imaging capability of water diffusion properties [24-26]. Specifically, tract-based spatial statistics (TBSS) derived from DTI is a delicate technique that conducts precise voxel-based white matter analysis and is suitable for implementation in multi-subject diffusion imaging-based studies [27]. In addition, TBSS avoids non-objective choice of regions of interest within hypothesis-based white matter areas [27]. Therefore, TBSS can provide comprehensive information on overall variations in the white matter's microstructure of the brain [27]. By using TBSS, several studies have demonstrated white matter changes in traumatic brain injuries; however, no study has reported abnormalities of white matter in isolated traumatic SAH patients [28-35].

In this study, we applied TBSS to investigate white matter abnormalities in patients with traumatic SAH.

Material and Methods

Subjects

Ten patients (6 men, 4 women; mean age 50.60±19.17 years; range, 23-79 years) were recruited according to the following inclusion criteria: (1) age: 20-80 years; (2) no history of previous head trauma or neurologic or psychiatric disease; (3) SAH due to head trauma, but no other definite brain lesion in the brain parenchyma (such as intracranial hemorrhage, intraventricular hemorrhage, hydrocephalus, or subdural hygroma), which was confirmed by a neuroradiologist; and (4) DTI data obtained after 4 weeks from hemorrhage onset. Ten age- and sex-matched healthy control subjects without previous history of psychiatric or neurologic disease or head trauma (6 men, 4 women; mean age 49.50±16.99 years, range 22-74 years) were also recruited as a control group. The demographic characteristics for the patient and control groups are listed in Table 1. Age or sex distribution identified no significant difference between the patient and control groups (P>0.05). This retrospective study was conducted following the requirements of the Declaration of Helsinki research guidelines and the recommendations of the Institutional Review Board of Yeungnam University Hospital. Signed informed consent was obtained from all of the subjects, and the study protocol was approved by the Institutional Review Board of Yeungnam University hospital (ethics approval number: YUMC-2021-03-014). In the case of patients with cognitive disorder or visual problem due to traumatic SAH, informed consent was provided through the caregiver.

Diffusion Tensor Imaging

DTI data were obtained at an average of 12.43±12.36 months after SAH onset by using a 1.5 T Philips Gyroscan Intera device (Hoffman-LaRoche, Best, Netherlands) with 32 non-collinear diffusion-sensitizing gradients by performing single-shot echo-planar imaging. For the 32 non-collinear diffusion-sensitizing gradients, 65 consecutive slices were obtained parallel to the anterior commissure – posterior commissure line [36]. Imaging parameters were as follows: acquisition matrix=96×96, reconstructed to matrix=192×192 matrix, field of view=240×240 mm, repetition time=10,398 ms, echo time=72 ms, echo-planning imaging factor=59 and b=1000 s/mm², slice gap=0, and slice thickness=2.5 mm [36]. Analysis of diffusion-weighted imaging data was conducted through the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (www.fmrib.ox.ac.uk/fsl). The head motion effects and image distortion were corrected by utilizing affine multi-scale two-dimensional registration [37].

Tract-Based Spatial Statistics

All data analyses were conducted utilizing the functional MRI evaluation tool through the FMRIB software library (FSL) [38]. Fractional anisotropy (FA) maps were created using a previously described method [27]. Using TBSS realized in the FSL, voxel-wise statistical analysis of the FA data was conducted [39]. To sort the FA data for all subjects into a common space, a non-linear registration algorithm (www.doc.ic.ac.uk/~dr/software) was utilized [38]. A mean FA image was generated and then thinned to make a mean FA skeleton showing the centroids of all areas common to the group subjects [38]. We then applied a threshold to and binarized the mean FA skeleton at an FA level >0.2, and the adjusted data were entered into the voxel-wise statistics process. Then, for each subject, the sorted FA data were reflected to the mean skeleton, and to assess the
FA values’ differences between each group, voxel-wise cross-subject statistics were acquired [38]. The results were adjusted to control the family-wise error rate to allow multiple comparisons after conducting threshold-free cluster enhancement [38]. To confirm the mean FA values of each subject and observe the differences for each tract, voxels recognized as TBSS were chosen. We assessed mean FA values within the skeleton and 48 regions of interest (ROIs) that were depending on crossing between the entire skeleton and the probabilistic white matter atlases of Johns Hopkins University for organizing the FA data in each of the white matter regions [38]. Differences in the FA values among the 48 ROIs were determined by subtracting the average FA value of the patient group from that of the control group. The obtained FA values’ differences were then arranged in descending order.

### Table 1. Demographic characteristics for the patient and control groups.

|                        | Patient group (n=10) | Control group (n=10) |
|------------------------|----------------------|----------------------|
| Age (years)            | 50.60±19.17          | 49.50±16.99          |
| Sex (Male: Female)     | 3: 8                 | 6: 4                 |
| Time to DTI scanning after onset (months) | 12.43±12.35 | NA |
| Loss of consciousness (n [%]) |                        |                      |
| <30 min                | 1 [0.1]              | NA                   |
| 30 min-24 h            | 4 [0.4]              | NA                   |
| >24 hr                 | 5 [0.5]              | NA                   |
| Post-traumatic amnesia (n [%]) |                        |                      |
| <1 day                 | 2 [0.2]              | NA                   |
| 1-7 days               | 2 [0.2]              | NA                   |
| >7 days                | 6 [0.6]              | NA                   |
| Initial GCS score (n [%]) |                      |                      |
| 13-15                  | 1 [0.1]              | NA                   |
| 9-12                   | 2 [0.2]              | NA                   |
| 3-8                    | 7 [0.7]              | NA                   |
| Traumatic brain injury (n [%]) |                        |                      |
| Mild                   | 1 [0.1]              | NA                   |
| Severe                 | 7 [0.7]              | NA                   |
| Cause (n [%])          |                      |                      |
| Passenger TA           | 1 [0.1]              | NA                   |
| Pedestrian TA          | 3 [0.3]              | NA                   |
| Slip/fall              | 4 [0.4]              | NA                   |
| Bicycle                | 2 [0.2]              | NA                   |

Values represent mean±standard deviation; DTI – diffusion tensor imaging; NA – not applicable; GCS – Glasgow Coma Scale; TA – traffic accident.

**Statistical Analysis**

Statistical analysis of the results was conducted using SPSS 21.0 for Windows (SPSS, Chicago, IL, USA). The chi-squared test was used to assess differences in the sex composition of the groups. The independent t test was performed to evaluate intergroup age differences and to examine the significance of FA values’ differences between the patient and control groups. Statistical significance was considered for P values <0.05.

**Results**

The voxel-wise FA values’ differences between the patient and control groups are listed in Table 2, and all of the ROIs are presented in ascending order, beginning with the ROI with the largest difference.
Table 2. Results from the region of interest-based analysis of fractional anisotropy values of the patient and control groups.

| Region                          | Patient group | Control group | Difference | p-Value |
|---------------------------------|---------------|---------------|------------|---------|
| Splenium of corpus callosum     | 0.62±0.03     | 0.66±0.02     | 0.04       | 0.002*  |
| Right posterior limb of internal capsule | 0.55±0.02     | 0.58±0.01     | 0.03       | 0.003*  |
| Right corticospinal tract       | 0.41±0.03     | 0.45±0.03     | 0.04       | 0.004*  |
| Left cerebral peduncle          | 0.56±0.04     | 0.60±0.02     | 0.04       | 0.007*  |
| Left superior corona radiata    | 0.40±0.02     | 0.44±0.02     | 0.04       | 0.008*  |
| Right superior corona radiata   | 0.40±0.02     | 0.42±0.02     | 0.03       | 0.038*  |
| Right posterior corona radiata  | 0.40±0.02     | 0.42±0.02     | 0.02       | 0.016*  |
| Genu of corpus callosum         | 0.48±0.03     | 0.51±0.02     | 0.03       | 0.019*  |
| Left corticospinal tract        | 0.41±0.05     | 0.46±0.03     | 0.05       | 0.023*  |
| Left posterior limb of internal capsule | 0.56±0.02     | 0.59±0.01     | 0.03       | 0.023*  |
| Body of corpus callosum         | 0.51±0.03     | 0.56±0.04     | 0.05       | 0.028*  |
| Right cingulum (hippocampus)    | 0.31±0.04     | 0.35±0.04     | 0.04       | 0.028*  |
| Left anterior limb of internal capsule | 0.45±0.03     | 0.48±0.02     | 0.03       | 0.028*  |
| Middle cerebellar peduncle      | 0.42±0.02     | 0.44±0.02     | 0.02       | 0.028*  |
| Left uncinate fasciculus        | 0.35±0.02     | 0.37±0.02     | 0.02       | 0.029*  |
| Left superior longitudinal fasciculus | 0.40±0.02     | 0.42±0.01     | 0.02       | 0.034*  |
| Left superior cerebellar peduncle | 0.45±0.05     | 0.50±0.03     | 0.05       | 0.041*  |
| Right superior cerebellar peduncle | 0.147±0.06    | 0.52±0.03     | 0.05       | 0.041*  |
| Left cingulum (cingulate gyrus) | 0.43±0.03     | 0.46±0.02     | 0.03       | 0.049*  |
| Right cerebral peduncle         | 0.56±0.03     | 0.59±0.02     | 0.03       | 0.059   |
| Left posterior corona radiata   | 0.39±0.02     | 0.41±0.02     | 0.02       | 0.059   |
| Left anterior corona radiata    | 0.35±0.04     | 0.39±0.03     | 0.04       | 0.070   |
| Pontine crossing tract          | 0.39±0.03     | 0.42±0.02     | 0.03       | 0.070   |
| Right anterior limb of internal capsule | 0.46±0.02     | 0.48±0.02     | 0.02       | 0.070   |
| Right superior fronto-occipital fasciculus | 0.37±0.05     | 0.41±0.06     | 0.04       | 0.096   |
| Left uncinate fasciculus        | 0.40±0.04     | 0.42±0.02     | 0.02       | 0.096   |
| Right tapetum                   | 0.33±0.03     | 0.35±0.04     | 0.02       | 0.096   |
| Left superior fronto-occipital fasciculus | 0.35±0.04     | 0.40±0.07     | 0.05       | 0.112   |
| Right anterior corona radiata   | 0.35±0.03     | 0.38±0.03     | 0.03       | 0.112   |
| Left fornix (crus)              | 0.32±0.04     | 0.35±0.03     | 0.03       | 0.131   |
| Right external capsule          | 0.34±0.02     | 0.36±0.02     | 0.02       | 0.131   |
| Right cingulum (cingulate gyrus) | 0.40±0.03     | 0.42±0.02     | 0.02       | 0.131   |
| Right medial lemniscus          | 0.52±0.03     | 0.54±0.02     | 0.02       | 0.151   |
| Left sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) | 0.42±0.02 | 0.44±0.03 | 0.02 | 0.151 |

* indicates statistical significance.
**Discussion**

The current study investigated microstructural differences in the subcortical white matter of the patient and control groups and obtained the following results: 1) FA values of the patient group were lower than those of the control group in 19 of the 48 ROIs: the corpus callosum [splenium (P=0.002), genu (P=0.019), body (P=0.028)], both posterior limbs of the internal capsule (right: P=0.003; left: P=0.023), both corticospinal tracts (right: P=0.004; left: P=0.023), both superior corona radiata (right: P=0.016; left: P=0.008), both superior cerebellar peduncles (right: P=0.041; left: P=0.041), the middle cerebellar peduncle (P=0.028), the left anterior limb of the internal capsule (P=0.028), the left external capsule (P=0.028), the right cingulum (hippocampus, P=0.028), the left superior longitudinal fasciculus (P=0.034), the left cingulum (cingulate gyrus, P=0.049), the left cerebral peduncle (P=0.007), and the right posterior corona radiata (P=0.016) (**Figure 1**). However, the FA values for the other 29 ROIs showed no significant differences between the patient and control groups (P>0.05).

The FA value, which reflects the grade of water diffusion’s directionality and represents the integrity of white matter (eg, indicative of axon diameter, fiber density, and myelination), used to assess white matter status [24-26]. A reduced FA value indicates decreased microstructural integrity of the neural structure of interest [24-26]. Our results show that 19 of the assessed 48 ROIs in the patient group had lower mean FA values than those of the control group, suggesting the existence of neural injuries in these 19 white matter areas. In addition, the 19 ROIs (the corpus callosum, the cingulum, the superior cerebellar peduncle, the middle cerebellar peduncle, the cerebral peduncle, the internal capsule, the corona radiata, the corticospinal tract, the external capsule, and the superior longitudinal fasciculus) showing significant differences between the patient and control groups are consistent with the brain areas vulnerable to DAI [40-42]. DAI can be reflective of a widespread traumatic injury such as that associated with fast acceleration – deceleration of the head in which

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**Table 2 continued.** Results from the region of interest-based analysis of fractional anisotropy values of the patient and control groups.

| Region                              | Patient group | Control group | Difference | p-Value |
|-------------------------------------|---------------|---------------|------------|---------|
| Fornix (column and body)            | 0.30±0.08     | 0.35±0.08     | 0.05       | 0.174   |
| Right posterior thalamic radiation (include optic radiation) | 0.49±0.05     | 0.52±0.03     | 0.03       | 0.174   |
| Right sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) | 0.44±0.03     | 0.46±0.03     | 0.02       | 0.174   |
| Left posterior thalamic radiation (include optic radiation) | 0.49±0.04     | 0.51±0.02     | 0.02       | 0.174   |
| Right uncinate fasciculus           | 0.41±0.04     | 0.43±0.02     | 0.02       | 0.174   |
| Right superior longitudinal fasciculus | 0.40±0.02     | 0.41±0.01     | 0.01       | 0.174   |
| Right fornix (crus)                 | 0.39±0.05     | 0.41±0.04     | 0.02       | 0.257   |
| Left tapetum                        | 0.26±0.02     | 0.27±0.02     | 0.01       | 0.257   |
| Left retrolenticular part of internal capsule | 0.49±0.02 | 0.50±0.02 | 0.01 | 0.290 |
| Left medial lemniscus               | 0.52±0.02     | 0.54±0.03     | 0.02       | 0.364   |
| Right retrolenticular part of internal capsule | 0.50±0.01 | 0.50±0.02 | 0.00 | 0.545 |
| Left inferior cerebellar peduncle   | 0.40±0.02     | 0.40±0.03     | 0.00       | 0.545   |
| Right inferior cerebellar peduncle  | 0.40±0.02     | 0.40±0.03     | 0.00       | 0.762   |

Values represent mean±standard deviation; * significant difference between the patient and control groups, P<0.05.
The shearing forces lead to mechanical axonal damage [40]. Many previous studies have reported that the common locations for DAI are the corpus callosum (especially the splenium), the subcortical white matter, and the brainstem [40-42]. In addition, injuries to several neural tracts, such as the cingulum, the corticospinal tract, the cerebellar peduncle, the superior and inferior longitudinal fasciculus, and the fornix, have also been detected in DAI patients by using DTI [15-23]. DAI is the chief cause of morbidity and mortality in traumatic brain injury patients [40]. Such patients frequently fall into a coma from the collision time, and survivors usually have severe disabilities. Based on our results, traumatic SAH patients appear to be accompanied by DAI; thus, traumatic SAH could be an indicator of the presence of severe brain injuries related to acute or excessive mechanical forces.

By using DTI, many studies have reported SAH-related neural tract injuries [36,43-55]. However, few studies have assessed the influence of SAH on the entire brain white matter, and recently, Jang et al (2020), by applying TBSS, demonstrated that spontaneous SAH following aneurysmal rupture can induce abnormalities in extensive areas of the subcortical white matter [36]. However, the majority of these previous studies are related to spontaneous aneurysmal SAH, and little has been reported on the neural injuries associated with traumatic SAH. Traumatic SAH is often caused by rupturing of the bridging veins or pial vessels that pass under the subarachnoid membrane or by blood outflow into the subarachnoid space from an adjacent cerebral contusion, rather than via the tear of an aneurysm [56]. Therefore, traumatic SAH would have different clinical symptoms and signs from those of spontaneous aneurysmal SAH, in which previous studies have suggested the symptoms are associated with the location of the hemorrhage, the amount of bleeding, the frequency of vasospasm, and the change in cerebral blood flow [57-59]. Our study also showed that the white matter injury caused by traumatic SAH differs from the widespread white matter injuries caused by aneurysmal SAH, and the traumatic SAH-related injuries were consistent with those reported in previous studies related to DAI. Further studies on the characteristics of neural injuries of traumatic SAH, which are different from those of spontaneous SAH, should be undertaken.

Many previous studies have used TBSS to identify the abnormalities of white matter in traumatic brain injury patients, and most of those traumatic injuries were accompanied by...
focal axonal injury or DAI [28-35]. In 2009, Perlbarg et al used TBSS to investigate white matter differences between 30 severe traumatic brain injury patients and 10 healthy controls, and observed FA value decrements in the inferior longitudinal fasciculus, the cerebral peduncle, the posterior limb of the internal capsule, and the posterior corpus callosum in the patient group [28]. In 2012, Messé et al compared structural integrity in 53 mild traumatic brain injury patients with that in 40 healthy controls and reported that the patient group had lower FA values than the control group in extensive brain regions, but primarily including the corpus callosum, the cerebellar peduncle, the internal and external capsules, the corona radiata and the thalamic radiation, the sagittal stratum, the fornix, and the superior longitudinal fasciculus [29]. In 2014, Xiong et al compared FA and mean diffusivity (MD) values of 20 mild traumatic brain injury patients with those of 25 healthy control subjects, and reported FA value decrements or MD value increments in the patient group in the uncinate fasciculus, the superior longitudinal fasciculus, the inferior longitudinal fasciculus, the internal capsule, and the corpus callosum [30]. In 2019, Choi et al compared white matter characteristics’ differences between 22 DAI patients and 30 healthy controls, and observed extensive diminution of the explicit myelin water fraction in DAI patients [31]. In 2020, Wright et al investigated white matter differences between 11 retired professional rugby league players with histories of sport-related concussion and 12 healthy controls, and reported FA value decrements or MD value increments in the superior longitudinal fasciculus, the corticospinal tract, the corpus callosum, and the uncinate fasciculus [32]. Furthermore, several other studies have also reported extended abnormalities of the white matter in traumatic brain injury patients contrasted to the white matter of the normal control group [33-35]. Aside from those studies, this is the first TBSS study to prove the abnormalities of white matter in isolated traumatic SAH patients.

Nonetheless, some limitations of our study should be considered. First, the small number of subjects in the study is a limitation. In addition, we could not acquire relevant clinical data because this study was conducted retrospectively. Hence, further prospective studies that include a massive number of subjects and collect more related clinical data are warranted. Second, TBSS collapses white matter tracts into a skeleton framework to mark the middle of the tract and merely projects the highest FA value acquired following the projection to that center; such an approach results in damage of information and the possibility of including data artifacts [60,61]. Third, TBSS methods automatically calculate the skeleton voxels’ statistics compared to the less-relevant voxels; thus, family-wise error correction is less punitive [61].

Conclusions

In conclusion, by applying a TBSS, we demonstrated white matter abnormalities in traumatic SAH patients. The corpus callosum and its adjacent neural structures, the brainstem and its adjacent neural structures, and the subcortical white matter that passes the long neural tracts were shown to have neural injuries in traumatic SAH patients, and these results are consistent with brain areas vulnerable to DAI. Therefore, traumatic SAH patients appeared to be accompanied by DAI, and traumatic SAH could be an indicator of the presence of severe brain injuries related to acute or excessive mechanical forces. Furthermore, we believe our results will be useful in future studies aimed at clarifying the pathophysiology of brain injury in traumatic SAH.

Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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