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Original Research

Glymphatic System Function in Patients with Transient Global Amnesia

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Abstract

Background: The purpose of this study was to examine glymphatic system function in patients with transient global amnesia (TGA), as well as to conduct a recurrence analysis. **Methods**: We enrolled patients with TGA and healthy controls from our hospital retrospectively. The patients and healthy controls were all scanned with the same 3T scanner, which included diffusion tensor imaging (DTI). We investigated the function of the glymphatic system using DTI analysis along the perivascular space (DTI-ALPS). The ALPS index was compared between patients with TGA and healthy controls, as well as between patients who had recurrent TGA events and those who had only a single TGA event. **Results**: Seventy-two patients with TGA and 53 healthy controls were enrolled. Sixty-five patients with TGA had a single TGA event, while seven patients had recurrent TGA events. The ALPS index did not differ significantly between patients with TGA and healthy controls (1.665 vs. 1.618, $p = 0.436$). The ALPS index, on the other hand, varied significantly according to recurrence in patients with TGA. The ALPS index was significantly higher in patients with recurrent TGA events compared to those with a single event (1.928 vs. 1.636, $p = 0.049$). **Conclusions**: We investigated the glymphatic system function in patients with TGA compared to healthy controls for the first time using the DTI-ALPS method. We discovered that these groups did not differ in terms of glymphatic system function. However, glymphatic system function in patients with TGA may differ according to recurrence. Additional research is required to substantiate these findings.

Keywords: glymphatic system; diffusion tensor imaging; transient global amnesia

1. Introduction

Transient global amnesia (TGA) is a sudden onset disease, in which episodic memory is anterogradely lost. During the ictal event, the patient repeats the same questions. The symptoms then return within 24 hours [1–3]. TGA has an annual incidence of between 3.4 and 10.4/100,000. The cause is unknown, but it is known to occur more frequently after the age of 50 [1–3]. In most cases, TGA symptoms develop once, but in rare cases, two or more relapses have been reported [4]. TGA is a common neurological disease, but its pathophysiologic mechansism has been still unknown [4].

The glymphatic system has been recently discovered in the brain as a pseudolymphatic system (referred to as the "g" lial and "lymphatic" systems). Unlike other parts of the body, the brain does not have a lymphatic system, but its name is derived from that glial cells act in the brain like the lymphatic system. The glymphatic system is critical for the removal of metabolic waste products in the brain by facilitating the exchange of interstitial fluid (ISF) and cerebrospinal fluid (CSF) [5,6]. It is thought to be a system that plays an important role because it cleans the brain. Recently, as the association between the glymphatic system function and neurodegenerative diseases such as Parkinson disease [7], dementia [8], and normal pressure hydrocephalus [9] has been reported, researches on the glymphatic system have been actively conducted. There are several tools that can look at glymphatic system function. Among these tools, tracer studies have been widely used to assess the glymphatic system function. They are conducted as follows; fluorescent tracers are injected into the cisterna manga and visualized using two-photon microscopy [10–12]. Additionally, MRI has been used to assess glymphatic system function by injecting gadolinium-based contrast agents as tracers intrathecally or intravenously [10–12]. Recently, apart from tracer methods, several other approaches to elucidating glymphatic system function have been used [10–12], including the method of diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) [13]. This method has the advantages of being non-invasive, not requiring a contrast agent, and being able to know the glymphatic system with a single shot imaging [13]. A few studies have been published to date that use the DTI-ALPS method to assess glymphatic system function in neurological disease [9,13–15]. However, there have been no studies using the DTI-ALPS method to investigate the alteration of glymphatic system function in patients with TGA.

The purpose of this study was to determine the function of the glymphatic system in patients with TGA using the DTI-ALPS method. We initially hypothesized that patients with TGA have lower glymphatic system function than healthy controls. Patients with TGA have no abnormalities in their brain MRI with visual inspection except hippocampal dot lesions on diffusion-weighted imaging (DWI). However, a recent quantitative MRI analysis has revealed several brain abnormalities in patients with TGA. A voxel-based morphometry study has demonstrated gray matter volume reduction in limbic structures, including hippocampus and cingulum, compared to healthy controls [16]. Another study has investigated the alterations of cortical morphology in patients with TGA, and found significantly altered cortical thickness in several brain regions, which were well correlated with the duration of TGA episodes [17]. Additionally, a DTI study has demonstrated the disrupted neuronal integrity in the cingulum fibers in patients with TGA [18]. Graph theory analysis using DTI MRI has been also applied to discover changes of structural connectivity in patients with TGA [19]. It has showed hubs reorganization, especially brain regions related with default-mode network, in TGA compared with healthy controls. All of these previous studies could suggest that there is a possibility of glymphatic system dysfunction in patients with TGA. This is supported by the fact that in patients with brain injury such as traumatic brain injury, glymphatic system function declines [20], and glymphatic system function and enlarged perivascular space shows good negative correlations [21].

Additionally, we analyzed glymphatic system function in patients with TGA according to recurrence in this study. TGA typically occurs only once in a patient's lifetime; however, in an estimated 6–10% of patients, TGA may occur repeatedly [3]. We have recently demonstrated that the functional network of patients with TGA differs according to the frequency of recurrence [22], and discovered significant structural covariance network changes as well as disruptions of the intrahippocampal circuit in TGA compared to control subjects, which is more pronounced when amnestic events recur [23]. As a result, we hypothesized that the glymphatic system function might be different in terms of recurrence. However, there has been no study evaluating glymphatic system function according to TGA recurrence. In the current study, we examined these two hypotheses.

2. Methods

2.1 Participants

The study was conducted retrospectively in a single tertiary hospital and was approved by the institutional review board. The following criteria were used to enroll patients with TGA: (1) From March 2018 to February 2021, a certified neurologist (Park KM) diagnosed patients with TGA using Hodges and Warlow's criteria at our hospital [24], (2) no structural lesions on brain MRI, with the exception of hippocampal dot lesions on DWI, (3) no epileptiform discharges on EEG, and (4) underwent DTI, which was included as a routine sequence for patients with TGA from March 2018 at our hospital. Clinical data were collected from patients with TGA through chart review. Then, we classified patients with TGA into two groups: those who experienced a single TGA event and those who experienced recurrent TGA events (i.e., those who had two or more TGA events).

Additionally, we included healthy controls who were age and sex matched and had no prior history of medical or neurological disease. These individuals' MRIs of the brain were normal. The data on these healthy controls were obtained from a previous study [25]. Those who did not want their data to be used in this study were excluded.

2.2 Diffusion Tensor Imaging Acquisition

The patients and healthy controls were all scanned DTI using the same MRI scanner, 3.0T (32-channel head coil, AchievaTx, Phillips Healthcare, Best, The Netherlands). In the patients with TGA, all of the MRI scanning were performed during postictal period. DTI parameters in a detail were already described in our previous studies [26,27].

2.3 ALPS Index Calculation

Although this was the first study using the DTI-ALPS method in patients with TGA, we have already conducted researches using this method in patients with other neurological disorders. Our previous article described the method for calculating the ALPS index in detail [15]. This was done using DSI studio program. To summarize, we opened the raw DTI data and applied a mask. We used the DTI method to reconstruct the fibers and determined their major diffusion direction. We determined the fiber orientation and diffusivities along the x, y, and z axes in the region of interest (ROI) adjacent to the lateral ventricle as voxel levels [13]. We chose one ROI for each fiber, including projection, association, and subcortical fibers, on the same x-axis from the several voxels that showed the fiber's maximum orientation. The ALPS index was calculated using the formula [13].

$$ALPS \text{ index} = \frac{\text{mean (Dxxproj, Dxxassoci)}}{\text{mean (Dyyproj, Dzzassoci)}} \quad (1)$$

The ALPS index was compared between TGA patients and healthy controls, as well as between patients with single and recurrent TGA events. In addition, we analyzed the difference of ALPS index between patients with recurrent TGA events and healthy controls.

2.4 Statistical Analyses

The Chi-square test, Fisher's exact test, Student's *t*-test or Mann-Whitney U test were used to compare the demographic and clinical characteristics, diffusivities, and ALPS index between two groups. We determined effect size by Cohen's *d* method. A two-tailed *p*-value of 0.05 was considered statistically significant. When comparing diffusivities between groups, we used the Bonferroni correction ($p = 0.005$ (0.05/9)). All statistical analyses were conducted with the MedCalc® Statistical Software version 20 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2021).

3. Results

3.1 Demographic and Clinical Characteristics of the Participants

Initially, a total of 83 patients met the clinical diagnostic criteria for TGA and had DTI MRI conducted with the same MRI scanner at our hospital. However, 11 patients were excluded from this study (nine patients had structural lesions on their brain MRI and two patients had poor image quality for analysis). Finally, 72 patients with TGA and 53 healthy controls were enrolled. The clinical characteristics of patients with TGA and healthy controls are shown in Table 1. Age and gender did not differ significantly between groups (59.1 vs. 57.2 years, $p = 0.166$; males, 29/72 vs. 23/53, $p = 0.727$). Sixty-five of the 72 patients with TGA experienced a single TGA event, while seven experienced recurrent TGA events (Six patients with two times of TGA events and one patient with three times of TGA events). The median time interval between the TGA events was six months (range 1–24 months) in the patients with recurrent TGA events. Between patients with a single TGA event and those with recurrent events, demographic and clinical characteristics were comparable (Table 1).

3.2 ALPS Index and Diffusivities

The differences in diffusivities and the ALPS index between patients with TGA and healthy controls are shown in Table 2. There were no significant differences in diffusivities or ALPS index between the groups (mean ALPS index = 1.665 vs. 1.618, mean difference = –0.046, 95 percent confidence interval (CI) of mean difference = –0.1644 to 0.0714, effect size = 0.143, $p = 0.436$) (Fig. 1). The ALPS index, on the other hand, varied significantly according to TGA recurrence. Patients with recurrent TGA events had a higher ALPS index (mean ALPS index = 1.928 vs. 1.636, mean difference = –0.291, 95 percent CI of mean difference = –0.582 to –0.000, effect size = 0.670, $p = 0.049$) (Fig. 1). There was no difference in diffusivities according to TGA recurrence. Additionally, in the comparison of the diffusivities and ALPS index between patients with recurrent TGA events and healthy controls, patients with recurrent TGA events had a higher ALPS index than healthy controls (mean ALPS index = 1.928 vs. 1.618, mean difference = –0.309, 95 percent CI of mean difference = –0.543 to –0.075, effect size = 0.774, $p = 0.010$). There were no significant differences in diffusivities between the groups.

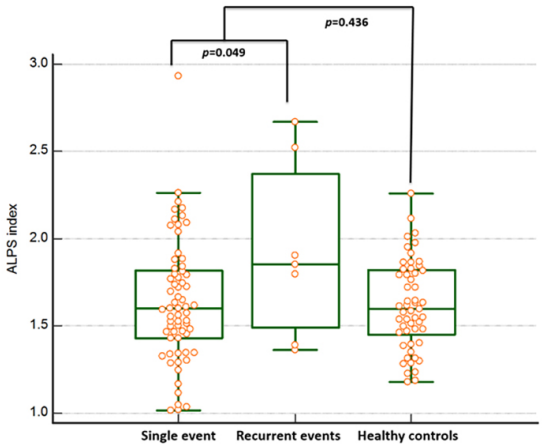

Fig. 1. Differences in the ALPS index between the groups.

The figure shows that the ALPS index in patients with recurrent TGA events is higher than that in patients with a single TGA event and the healthy controls. This suggests that the glymphatic system function differs according to the TGA recurrence. Nevertheless, in general, there were no differences in the ALPS index between patients with TGA and the healthy controls. This means that the glymphatic system function does not differ between the patients with TGA as a whole group and the healthy control group.

3.3 Correlation Analysis between ALPS Index and Clinical Characteristics

In patients with TGA, there was no significant correlation between the ALPS index and clinical characteristics such as age ($r = –0.028$, $p = 0.816$) and amnesia duration ($r = 0.056$, $p = 0.676$).

4. Discussion

We evaluated glymphatic system function in patients with TGA for the first time using the DTI-ALPS method based on DTI. The ALPS index was not different between patient with TGA and healthy controls, which indicating that patients with TGA had comparable glymphatic system function to healthy controls. Additionally, there was no significant correlation between clinical characteristics, such as age and amnesia duration in TGA, and the ALPS index, suggesting no association between glymphatic system function and TGA clinical symptoms. However, we found the difference in ALPS index between patients with recurrent TGA events and those with a single TGA event, suggesting that the function of the glymphatic system varied according to the frequency of TGA events. Glymphatic system function was higher in patients with recurrent TGA events compared to patients with a single event.

Table 1. The demographic and clinical characteristics of patients with TGA and the healthy controls.

	Patients with TGA (N = 72)	Healthy controls (N = 53)	*p*-value
Age, years (± SD)	59.1 ± 5.6	57.2 ± 9.4	‡0.165
Male, n (%)	29 (40.2)	23 (43.3)	*0.727
	Patients with recurrent TGA events (N = 7)	Patients with a single TGA event (N = 65)	*p*-value
Age, years (± SD)	57.2 ± 7.8	59.3 ± 5.4	‡0.371
Male, n (%)	5 (71.4)	24 (36.9)	†0.109
Focal slow waves in EEG, n (%)	1 (14.2)	10 (15.3)	†1.000
Hippocampal dot lesion on DWI, n (%)	3 (42.8)	21 (32.3)	†0.679
Duration of amnesia, hours (range)	4 (0.5–12)	3.5 (0.5–24)	§0.865
Precipitation factor	3 (42.8)	40 (61.5)	†0.428
Emotional stress, n	1	22	
Physical activity, n	2	8	
Temperature change, n	0	10	
Past medical history	2 (28.5)	30 (46.1)	†0.451
Hypertension, n	1	13	
Dyslipidemia, n	1	7	
Diabetes, n	0	5	
Others, n	0	10	

TGA, transient global amnesia; EEG, electroencephalography; DWI, diffusion-weighted imaging; Statistical analyses with *Chi-square test, †Fisher's exact test, ‡Student's *t*-test, or §Mann-Whitney U test.

In this study, there was no difference in glymphatic system function between patients with TGA and the healthy controls, evidenced by the DTI-ALPS method. In addition, the ALPS index value (1.665) in patients with TGA in this study was not low even when compared with other studies [9,13]. Although it is difficult to determine the exact reasons for this result, two possibilities can be considered. First, glymphatic system function in patients with TGA could actually be comparable to that in healthy controls. This is well-known that the prognosis of TGA is usually good, and patients recover from amnestic symptoms within 24 hours. Although one previous study has shown an increased possibility of dementia after a TGA attack [28], most of other studies have revealed no increase in the likelihood of developing dementia in patients with TGA [29]. In fact, there is another debate about the prognosis of TGA. Hsieh *et al*. [30] have conducted a control cohort study with an 8-year follow-up period involving 185 patients with TGA and found that TGA was associated with an increased long-term risk of epilepsy. However, another study has indicated that having an episode of TGA does not increase the risk of subsequent seizures [29]. It is generally known that TGA shows good prognosis and it is not a risk factor for neurological diseases such as stroke, epilepsy, or dementia. Furthermore, there is controversy about the issue of internal jugular valve insufficiency. Some studies have demonstrated the presence of jugular valve insufficiency in patients with TGA [31–33]; nevertheless, another study has shown no such difference between patients with TGA and the healthy control group [34]. In addition, a study has found that although there was a significantly higher rate of internal jugular valve insufficiency in patients with TGA compared to controls, no differences in intracranial venous circulation were discovered between groups, including an effect of body position, which could result in normal glymphatic system function among patients with TGA [31]. However, internal jugular valve insufficiency is not associated with disturbed intracranial venous hemodynamics in patients with TGA [35,36]. Quantitative structural imaging analysis studies are also controversial. Some studies have found significant quantitative structural alterations in the brain [16,17] as well as connectivity network changes [19,23] in patients with TGA compared to healthy controls. However, another study using neurite orientation dispersion, density imaging, and arterial spin labeling examined whether or not the microstructure and perfusion status of the hippocampus showed any obvious microstructural or perfusion abnormalities in patients with TGA was negative [37]. All of these suggest that TGA can be a benign disease, such that there could be no abnormality in the glymphatic system function, which is supported by the present study. A previous systematic review, which assessed the long-term prognosis of TGA, found a benign prognosis with respect to the vascular sequelae, but a lack of relevant evidence supporting an overall favorable prognosis, especially when considering the outcomes of dementia and epilepsy. Further researches are needed [38]. The second possibility is that although there could be glymphatic system dysfunction in patients with TGA, our study failed to find it. If our study findings indicate false-negative results, the first reason that could explain this is that all of the MRIs of our patients were taken after the TGA symptoms were over. Because TGA symptoms improve within 24 hours, it is very difficult to perform MRI during the ictal TGA period. An-

Table 2. Differences in the diffusivities and ALPS index between patients with TGA and the healthy controls.

	Patients with TGA (N = 72)		Healthy Controls (N = 53)		
	Mean	SD	Mean	SD	*p*-value
Projection fiber					
Dxx	0.000559	0.000094	0.000590	0.000076	0.045
Dyy	0.000389	0.000105	0.000420	0.000096	0.087
Dzz	0.001069	0.000103	0.001083	0.000118	0.483
Association fiber					
Dxx	0.000600	0.000101	0.000636	0.000100	0.050
Dyy	0.001116	0.000123	0.001134	0.000150	0.470
Dzz	0.000332	0.000096	0.000354	0.000091	0.199
Subcortical fiber					
Dxx	0.001079	0.000162	0.001077	0.000158	0.950
Dyy	0.000645	0.000171	0.000656	0.000189	0.732
Dzz	0.000611	0.000159	0.000647	0.000204	0.273
ALPS index	1.665	0.375	1.619	0.254	0.436
	Patients with recurrent TGA events (N = 7)		Patients with a single TGA event (N = 65)		
	Mean	SD	Mean	SD	*p*-value
Projection fiber					
Dxx	0.000611	0.000080	0.000553	0.000095	0.124
Dyy	0.000345	0.000091	0.000393	0.000106	0.246
Dzz	0.001060	0.000097	0.001070	0.000105	0.803
Association fiber					
Dxx	0.000611	0.000078	0.000599	0.000104	0.776
Dyy	0.001078	0.000096	0.001120	0.000125	0.396
Dzz	0.000316	0.000116	0.000334	0.000094	0.633
Subcortical fiber					
Dxx	0.001074	0.000164	0.001080	0.000163	0.929
Dyy	0.000689	0.000242	0.000640	0.000164	0.477
Dzz	0.000654	0.000231	0.000606	0.000151	0.454
ALPS index	1.928	0.506	1.637	0.351	0.049
	Patients with recurrent TGA events (N = 7)		Healthy Controls (N = 53)		
	Mean	SD	Mean	SD	*p*-value
Projection fiber					
Dxx	0.000611	0.000080	0.000590	0.000076	0.506
Dyy	0.000345	0.000091	0.000420	0.000096	0.053
Dzz	0.001060	0.000097	0.001083	0.000118	0.619
Association fiber					
Dxx	0.000611	0.000078	0.000636	0.000100	0.517
Dyy	0.001078	0.000096	0.001134	0.000150	0.347
Dzz	0.000316	0.000116	0.000354	0.000091	0.313
Subcortical fiber					
Dxx	0.001074	0.000164	0.001077	0.000158	0.957
Dyy	0.000689	0.000242	0.000656	0.000189	0.675
Dzz	0.000654	0.000231	0.000647	0.000204	0.929
ALPS index	1.928	0.506	1.619	0.254	0.010

TGA, transient global amnesia; Dxx, diffusivity along the x-axis; Dyy, diffusivity along the y-axis; Dzz, diffusivity along the z-axis. All of the statistical analyses were conducted with Student's *t*-test.

other possibility is that we used the DTI-ALPS method to evaluate glymphatic system function, which is a method that uses DTI, and DTI is a modality that assesses structural anomalies rather than functional abnormalities. Our study was not the result of investigating glymphatic system functions in patients with TGA using a transitional tracer. Since both of these possibilities are plausible, future researches using other methods in patients with TGA are needed in order to confirm our results.

We interestingly found that glymphatic system function differed according to the recurrence of TGA events; in particular, the ALPS index was higher in patients with recurrent TGA events than in patients with a single event, indicating higher glymphatic system function in the TGA recurrence group. Additionally, patients with recurrent TGA events had a higher ALPS index than healthy controls. Sev-

eral studies have investigated the risk factors for TGA recurrence and suggest that recurrence is associated with female, depression, short duration of amnesia, hippocampal dot lesion on DWI, early age of onset, and history of migraine and head injury [39–41]. However, to date, no studies have investigated the association between glymphatic system function and recurrence in patients with TGA. In fact, our findings showing that glymphatic system function was higher in patients with recurrent TGA events than in patients with a single event were unexpected. The plausible explanation was compensation effects or type 1 error, although we do not know the exact cause of this result. Since all of our patients' MRI scans were taken after the ictal TGA period, we believe that glymphatic system function was more activated to restore the damaged brain function in the recurrent TGA events group than in the single TGA event group. However, to confirm this, MRI is required before the TGA event occurs, so it is not clear. Another possibility is that although it had statistically significant, the possibility of type 1 error could not be excluded. This is because the number of patients with recurrent TGA was very small with only seven TGA patients, and the *p*-value was 0.049, which was meaningful as a borderline. Considering that there was no statistical difference in the ALPS index between patients with TGA as a whole and healthy control, even a small difference in the ALPS index according to the recurrence of TGA events may not have any clinical significance. To confirm our findings, MRI scanning with large cohorts during the ictal TGA period is necessary, and a follow-up MRI is also required.

Our study is the first investigation on glymphatic system function in patients with TGA using the DTI-ALPS method that also involved a large sample size. However, there were some study limitations. First, this study was conducted at one hospital. Because our hospital is a tertiary hospital, our study results cannot be applied to all patients with TGA and therefore cannot be generalized. In addition, although we enrolled a relatively large number of patients with TGA, the sample size for patients with recurrent TGA events was relatively small. This is a result of the low incidence of recurrence in TGA events. Nevertheless, in statistical analysis, it is a well-known fact that the good balance between the two groups being compared is needed. Second, glymphatic system function is reportedly different during the waking and sleeping states; in particular, glymphatic system function is increased during deep sleep [42]. By contrast, all of our patients had their MRIs taken during the day while they were awake, because our hospital allows MRI scans during the day. If MRI scans had been taken while the patients were sleeping, the results could be different from the present findings. It is not known whether the function of the glymphatic system function observed in structural MRI, such as DTI, rather than functional MRI, differs depending on the day and night. To confirm this fact, two MRI scans are needed in the same patient, both daytime and nighttime. Third, because this study is a retrospective study, it was difficult to accurately determine the time from TGA symptom onset to MRI taken. Therefore, the difference in glymphatic system function according to time interval could not be analyzed. A prospective study will be needed.

5. Conclusions

For the first time, we investigated glymphatic system function in patients with TGA compared to healthy controls using the DTI-ALPS method. We found that there was no difference in glymphatic system function between these groups. However, glymphatic system function may differ according to TGA recurrence. Further studies are needed to confirm these findings.

Author Contributions

Conceptualization—KMP and DAL; methodology—KMP; validation—DAL and BSP; formal analysis—KMP; data curation—SP, YJL and JK; writing—original draft preparation—DAL, BSP and KMP; writing—review and editing—KMP; supervision—KMP.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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