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ORIGINAL ARTICLE

Glymphatic system dysfunction in temporal lobe epilepsy patients with hippocampal sclerosis

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Abstract

Objective: This study aimed to evaluate glymphatic system function in temporal lobe epilepsy (TLE) patients with hippocampal sclerosis (HS) in comparison to healthy controls, using diffusion tensor imaging (DTI)-analysis along the perivascular space (ALPS) method. We hypothesized that there is glymphatic system dysfunction in TLE patients with HS.

Methods: We retrospectively enrolled 25 TLE patients with HS and 26 age- and sex-matched healthy controls. All participants underwent DTI with the same 3T magnetic resonance imaging scanner, and the DTI-ALPS index was calculated. We evaluated the differences in the DTI-ALPS index between TLE patients with HS and healthy controls. Moreover, we evaluated the correlation between the DTI-ALPS index and clinical characteristics of epilepsy, including age, age at seizure onset, duration of epilepsy, and number of anti-seizure medications (ASMs).

Results: There was a difference in the DTI-ALPS index between TLE patients with HS and healthy controls. The DTI-ALPS index in TLE patients with HS was lower than that in healthy controls (1.497 vs. 1.668, $P = .015$). However, there was no difference in the DTI-ALPS index between the newly diagnosed TLE patients with HS and the chronic TLE patients with HS. The DTI-ALPS index was negatively correlated with age ($r = -0.420$, $P = .036$). However, the DTI-ALPS index was not correlated with other clinical characteristics, including age at seizure onset, duration of epilepsy, and number of ASMs.

Significance: Our findings showed that the DTI-ALPS index was significantly lower in TLE patients with HS than in healthy controls, indicating the presence of glymphatic system dysfunction in TLE patients with HS. Our study also suggests that the DTI-ALPS method may be useful for evaluating glymphatic system function in epilepsy.

1 | INTRODUCTION

The glymphatic pathway is a highly organized interconnected glial-lymphatic fluid transport system that works as a waste drainage system in the brain through a unique anatomical structure.[1,2] Cerebrospinal fluid (CSF) flow is generated by the convective differences between the perivascular and parenchymal interstitial spaces, and metabolite elimination in the brain occurs through it.[1,3] Thus, the circulation of interstitial fluid (ISF) and its bulk flow plays an important role in central nervous system waste elimination. The glymphatic system function has been intensively studied in various neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury, and normal pressure hydrocephalus (NPH).[1,4] The studies have consistently shown glymphatic system dysfunction in these neurodegenerative diseases.[1]

After a two-photon microscopic study in a mice model revealed the existence of a glymphatic pathway,[4] imaging for the glymphatic system has been successfully achieved by tracking radioactive tracers in the animal brain in vivo.[5,6] Generally, in human studies, intrathecal injection of a tracer is followed by tracking using magnetic resonance imaging (MRI).[7–9] However, there is a need for more safe and non-invasive imaging approaches for visualizing glymphatic system function in the human brain.[10] A recent study has newly proposed a diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) method as a non-invasive and safe image-analysis method to discover glymphatic system function.[11–14] The DTI-ALPS method evaluates the motion of water molecules in the direction of the perivascular space by measuring diffusivity.[11] The medullary veins run perpendicular to the ventricular wall at the level of the lateral ventricle body, and the perivascular space runs in the same direction as the medullary veins, which is latero-to-lateral. On the plane of this region, projection fibers run head-to-foot, primarily adjacent to the lateral ventricle, while superior longitudinal fascicles, representing association fibers, run anterior-posterior. Outside of the superior longitudinal fascicles, subcortical fibers predominantly run latero-to-lateral in subcortical areas. As a result, the perivascular space is perpendicular to the projection fibers and superior longitudinal fascicles in this region. Due to the fact that major fiber tracts do not run parallel to the perivascular space's direction, this conformation of the perivascular space and major fibers in this area enables nearly independent analysis of diffusivity along the perivascular space's

Key Points

- We hypothesized that there is glymphatic system dysfunction in temporal lobe epilepsy patients with hippocampal sclerosis.
- Diffusion tensor imaging (DTI)-analysis along the perivascular space (ALPS) was used to assess glymphatic system function.
- DTI-ALPS index was significantly lower in temporal lobe epilepsy patients with hippocampal sclerosis than in healthy controls.
- A lower DTI-ALPS index indicates the presence of glymphatic system dysfunction.
- DTI-ALPS may be useful for evaluating functioning of glymphatic system in epilepsy.

direction.[11] The diffusivities along the x-axis in the projection and association fibers express water diffusion along the perivascular space without interference from neural fibers, thus reflecting the glymphatic activities. In contrast, the diffusivities along the x-axis in the subcortical fibers would not reflect pure perivascular water diffusion, since the subcortical neural fibers pass parallel to the perivascular flow and obscure glymphatic diffusion. Furthermore, the diffusivities along the y-axis and z-axis that are orthogonal to the perivascular flow would not reflect glymphatic diffusion. Thus, it is appropriate to use the diffusivities along the x-axis in the projection and association fibers in the DTI-ALPS method with a correction for the diffusivities along the y-axis in the projection fiber and the diffusivities along the z-axis in the association fiber, to evaluate the diffusivity along the perivascular space.[14] Therefore, decreased DTI-ALPS index indicates a reduction in perivascular diffusivity, suggesting glymphatic system dysfunction. The DTI-ALPS method does not need contract injection and it has good inter-observer agreements.[11–14] Therefore, it is very effective for clinical application in human. The feasibility of this non-invasive DTI-ALPS method has been also demonstrated in recent studies that evaluated glymphatic system function in various neurological conditions.[11,13,14]

Temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) is a common type of epilepsy referred for epilepsy surgery, because it is often refractory to anti-seizure medications (ASMs).[15,16] The functioning status of the glymphatic

system has been known to affect the initiation and termination of seizures.[17] Previous studies have revealed that after sustained epileptic seizures, glutamate overproduction, oxidative stress, and proinflammatory mediators can induce and sustain blood-brain barrier (BBB) disruptions[18] and may contribute to abnormal CSF-ISF circulations.[19] Considering local peri-ictal abnormality in TLE with HS, hippocampal swelling, BBB breakdown, and altered neurovascular coupling are also commonly detected in TLE with HS.[20] Altered permeability and endothelial damage of blood vessels due to BBB disruptions can cause abnormal neuronal activity.[21] In the epileptic brain, glutamate accumulation and phosphorylated tau protein overexpression are affected by ISF clearance.[22] Long-term pathological changes in the epileptic brain may modify the ISF flow, reduce the clearance system, and lead to the accumulation of toxic molecules.[20] These findings suggest that there is glymphatic system dysfunction in TLE patients with HS.

Therefore, this study aimed to evaluate glymphatic system dysfunction in TLE patients with HS in comparison to healthy controls, using the DTI-ALPS method. We also investigated the association between glymphatic system function and the clinical characteristics of epilepsy.

2 | METHODS

2.1 | Participants

This study was approved by the institutional regional board of our hospital. We retrospectively enrolled TLE patients with HS based on the following criteria: (1) presence of typical ictal semiology compatible with TLE; (2) presence of ictal epileptiform discharges originating from the temporal lobe on electroencephalogram; (3) presence of typical HS features on brain MRI, including high signal intensity of the hippocampus on fluid-attenuated inversion recovery and hippocampal atrophy; (4) those who underwent DTI at our hospital from March 2018 to March 2021, (5) absence of any other brain lesions except HS; and (6) absence of any other medical or neurological diseases except epilepsy (Figure S1). We also excluded patients with bilateral HS. We obtained the information about clinical characteristics, such as age, sex, age at seizure onset, duration of epilepsy (time from the first seizure onset to the time MRI was taken), and number of ASMs at the time of MRI, of TLE patients with HS from medical records of our hospital. In addition, we classified TLE patients with HS into two groups: newly diagnosed epilepsy with drug-naive status and chronic epilepsy with ASMs.

We also enrolled age- and sex-matched healthy controls. They had a normal brain MRI on visual inspection and had no any other medical or neurological diseases.

2.2 | Magnetic resonance imaging acquisition and processing

DTI was performed using the same scanner (3.0T, 32-channel head coil, AchievaTx, Phillips Healthcare, Best, The Netherlands) for all patients and healthy controls. It was performed using spin-echo single-shot echo-planar pulse sequences with 32 different diffusion directions (repetition time/echo time, 8620/85 ms; flip angle, 90°; slice thickness, 2.25 mm; acquisition matrix, 120 × 120; field of view, 240 × 240 mm^2; and b-value, 1000 s/mm^2).

We used the DSI studio program that included open-source images (version 2021 May, http://dsi-studio.labsolver.org) for preprocessing of brain MRI to correct the eddy current and phase distortion artifact, set up a mask (thresholding, smoothing, and defragments), and perform reconstruction using DTI.

2.3 | Calculation of the diffusion tensor imaging analysis along the perivascular space index

We recently described the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) method in a previous study.[23] Briefly, we drew a square region of interest (ROI) in the contralateral side of HS in order to exclude the effects of HS on the diffusivities in the fibers. Then, we obtained the fiber orientation and diffusivities of the three directions along the x-, y-, and z-axes as voxel levels at the ROI. Among the several voxels, we selected one ROI for each fiber on the same x-axis (projection, association, and subcortical fibers) that showed the maximum orientation in each fiber. The DTI-ALPS index was calculated using the following formula (Figure 1):

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

where Dxxproj is the diffusivity along the x-axis in the projection fiber, Dxxassoci is the diffusivity along the x-axis in the association fiber, Dyyproj is the diffusivity along the y-axis in the projection fiber, and Dzzassoci is the diffusivity along the z-axis in the association fiber.

2.4 | Statistical analyses

Statistical comparisons were conducted using the chi-squared test or Fisher's exact test for categorical variables and the independent samples t-test or Mann–Whitney U test for continuous variables according to normal distribution tested with the Shapiro–Wilk method. Categorical variables are expressed as numbers and percentages. Continuous variables
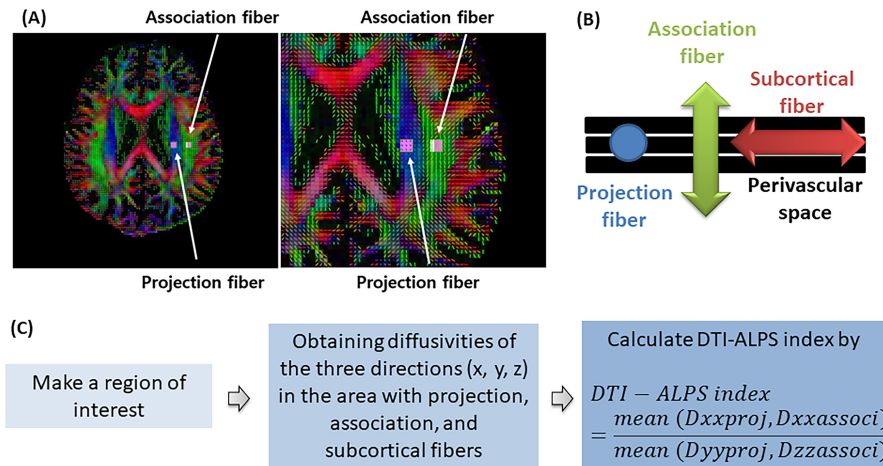
FIGURE 1 Calculation of the DTI-ALPS index. (A) Place the region of interests in the areas with projection and association fibers, (B) The schematic relation and directions of the perivascular space and three fibers including projection, association, and subcortical fibers, and (C) Flowchart illustrating the process of calculating DTI-ALPS index. Figure is generated from our previous study[31] and modified. Dxxproj: diffusivity along the x-axis in the projection fiber; Dxxassoci: diffusivity along the x-axis in the association fiber; Dyyproj: diffusivity along the y-axis in the projection fiber; Dzzassoci: diffusivity along the z-axis in the association fiber

with normal distribution are represented as mean values with standard deviations, and continuous variables without normal distribution are represented as median values with interquartile range. Statistical significance was defined as a two-tailed P-value <.05. Multiple corrections were applied when we performed statistical analysis for diffusivities along the axis in the fibers (Bonferroni correction, $P = .0055$ [0.05/9]). All statistical analyses were performed using MedCalc® Statistical Software version 20 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2021).

3 | RESULTS

3.1 | Participants

Table 1 shows the demographic and clinical characteristics of TLE patients with HS and healthy controls. The age and sex were not different between the TLE patients with HS and healthy controls (age, 44.3 vs. 44.8 years, $P = .858$; male, 13/25 [52.0%] vs. 11/26 [42.3%], $P = .492$). Of the 26 TLE patients with HS, six (24.0%) were newly diagnosed with epilepsy, whereas 19 (76.0%) had chronic epilepsy. The age and sex of newly diagnosed TLE patients with HS were not significantly different from those of chronic patients with the same condition (age, 39.6 vs. 45.8 years, $P = .308$; male, 1/6 [16.7%] vs. 12/19 [63.1%], $P = .073$).

3.2 | Diffusivities along the axis in the fibers

There were no significant differences in diffusivities along the x-, y-, and z-axes in the projection, association, and subcortical fibers between TLE patients with HS and healthy controls (Table 2). In addition, the diffusivities along the x-, y-, and z-axes in the projection, association, and subcortical fibers in newly diagnosed TLE patients with HS were not different from those in chronic TLE patients with HS (Table 3).

3.3 | Diffusion tensor imaging analysis along the perivascular space index

There was a significant difference in the DTI-ALPS index between TLE patients with HS and healthy controls. The DTI-ALPS index in TLE patients with HS was lower than that in healthy controls (1.497 vs. 1.668, $P = .015$) (Figure 2). However, there was no significant difference in the DTI-ALPS index between the newly diagnosed TLE patients with HS and the chronic TLE patients with HS (1.496 vs. 1.469, $P = .993$) (Figure 3).

3.4 | Correlation between the diffusion tensor imaging analysis along the perivascular space index and clinical characteristics

The DTI-ALPS index was negatively correlated with age ($r = -0.420$, $P = .036$) in TLE patients with HS. However, the DTI-ALPS index was not significantly correlated with other clinical characteristics, including age at seizure onset, duration of epilepsy, and number of ASMs ($r = -0.294$, $P = .082$; $r = -0.010$, $P = .969$; and $r = -0.262$, $P = .205$, respectively).

In healthy control, the DTI-ALPS index was also negatively correlated with age ($r = -0.308$, $P = .042$).

TABLE 1 Demographic and clinical characteristics of TLE patients with HS and healthy controls

	TLE patients with HS (N = 25)	Healthy controls (N = 26)	*P*-value
Mean age, years	44.3 ± 12.6	44.8 ± 5.3	.858
Male, n (%)	13 (52.0)	11 (42.3)	.492
Mean age of onset, years	32.2 ± 17.2		
Median duration of epilepsy, months	60 (0-246)		
Right HS, n (%)	11 (44)		
Median number of ASMs, n	2 (0.75-4)		
	Newly diagnosed TLE patients with HS (N = 6)	**Chronic TLE patients with HS (N = 19)**	*P*-value
Mean age, years	39.6 ± 16.3	45.8 ± 11.4	.308
Male, n (%)	1 (16.7)	12 (63.1)	.073
Mean age of onset, years	39.3 ± 16.1	28.7 ± 17.2	.229
Median duration of epilepsy, months	0 (0-0)	168 (60-324)	.001
Right HS, n (%)	3 (50)	8 (42)	1.000
Median number of current ASMs, n	0 (0-0)	4 (2-4)	<.001
Current ASMs, n (%)			
LTG		12 (63.1)	
LEV		12 (63.1)	
VPA		9 (47.3)	
LCM		8 (42.1)	
TPK		7 (36.8)	
PER		5 (26.3)	
CBZ		3 (15.7)	
ZNS		2 (10.5)	
PRB		2 (10.5)	
Oxcarbazepine		1 (5.2)	

Abbreviations: ASMs, anti-seizure medications; CBZ, carbamazepine; HS, hippocampal sclerosis; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PER, perampanel; PRB, pregabalin; TLE, temporal lobe epilepsy; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

4 | DISCUSSION

In this study, we investigated glymphatic system function in TLE patients with HS in comparison with healthy controls, using the DTI-ALPS method. The main finding of this study was that the DTI-ALPS index was significantly lower in TLE patients with HS than in healthy controls, indicating glymphatic system dysfunction in TLE patients with HS. In addition, the DTI-ALPS index was negatively correlated with age, suggesting a decline in glymphatic system function with age, in TLE patients with HS.

With the increasing interest in the glymphatic system, many studies on neurological diseases have been conducted recently. Decreased amyloid β clearance plays a role in the pathophysiology of AD,[24] and the decreased clearance of phosphorylated tau is associated with chronic traumatic encephalopathy.[25] Similarly,

impaired interstitial solute clearances with abnormal CSF-ISF communication can be observed in the epileptic brain.[20] With the loss of BBB integrity occurring due to an ictal event, serum solute shifts locally in the brain parenchyma and water accumulation is produced by changes in ISF ionic composition.[26] Long-term pathological changes may modify the ISF flow, causing a decreased clearance system along with accumulation of toxic molecules in the brain.[20] Interestingly, phosphorylated tau is identified in surgically removed brain specimens of patients with epilepsy. The distribution of phosphorylated tau in patients with epilepsy is found across the cortical neurons, perivascular regions around the penetrating pial vessels, and meninges; and extracellular phosphorylated tau is also distributed parallel to venules.[27] This distribution of phosphorylated tau in the brain is not similar with immunoglobulin G or albumin,

TABLE 2 The differences of the diffusivities along the axis in the fibers between TLE patients with HS and healthy controls ($\times 10^{-3}$ mm^2/s)

	TLE patients with HS (N = 25)	Healthy controls (N = 26)	*P*-value
Projection fiber			
Dxx	0.564 ± 0.122	0.600 ± 0.088	.237
Dyy	0.397 ± 0.110	0.416 ± 0.111	.532
Dzz	1.089 ± 0.170	1.067 ± 0.129	.615
Association fiber			
Dxx	0.602 ± 0.092	0.632 ± 0.092	.260
Dyy	1.172 ± 0.178	1.153 ± 0.131	.673
Dzz	0.396 ± 0.113	0.340 ± 0.076	.044
Subcortical fiber			
Dxx	1.062 ± 0.161	1.079 ± 0.165	.704
Dyy	0.660 ± 0.166	0.632 ± 0.171	.558
Dzz	0.651 ± 0.112	0.581 ± 0.118	.036

Abbreviations: Dxx, diffusivity along the x-axis; Dyy, diffusivity along the y-axis; Dzz, diffusivity along the z-axis; HS, hippocampal sclerosis; TLE, temporal lobe epilepsy.

TABLE 3 The differences of the diffusivities along the axis in the fibers between newly diagnosed TLE patients with HS and chronic TLE patients with HS ($\times 10^{-3}$ mm^2/s)

	Newly diagnosed TLE patients with HS (N = 6)	Chronic TLE patients with HS (N = 19)	*P*-value
Projection fiber			
Dxx	0.619 ± 0.055	0.547 ± 0.133	.214
Dyy	0.455 ± 0.087	0.378 ± 0.112	.140
Dzz	1.173 ± 0.184	1.062 ± 0.161	.165
Association fiber			
Dxx	0.659 ± 0.116	0.584 ± 0.079	.085
Dyy	1.206 ± 0.190	1.161 ± 0.179	.602
Dzz	0.403 ± 0.100	0.394 ± 0.119	.865
Subcortical fiber			
Dxx	1.035 ± 0.105	1.071 ± 0.176	.647
Dyy	0.604 ± 0.171	0.678 ± 0.165	.352
Dzz	0.623 ± 0.132	0.660 ± 0.108	.494

Abbreviations: Dxx, diffusivity along the x-axis; Dyy, diffusivity along the y-axis; Dzz, diffusivity along the z-axis; HS, hippocampal sclerosis; TLE, temporal lobe epilepsy.

which is an extravasation marker. In addition, perivascular phosphorylated tau does not extend radially from the vessel, but rather follows longitudinal paravascular tracks, which suggests that the presence of elevated phosphorylated tau is related to poor clearance of waste from the brain.[20] Furthermore, seizure termination by glymphatic system rinsing is measured by calculating changes in the concentration of glutamate in interictal and ictal phases.[28]

The DTI-ALPS method was used to evaluate glymphatic system function in several neurodegenerative disorders. In a study on patients with AD, a significant correlation between the DTI-ALPS index and the disease severity was revealed.[11] In a study comparing the DTI-ALPS index between patients with PD and patients with essential tremor, a lower DTI-ALPS index was identified in the PD group than in those with essential tremor.[29] A recent study measured the DTI-ALPS index in patients with PD, and they found that patient groups of PD associated with mild cognitive impairment or dementia showed a significantly lower DTI-ALPS index than that observed in normal controls.[30] In the NPH study, the DTI-ALPS index was significantly lower in patients with NPH than that in healthy controls.[14] It is, therefore, meaningful to
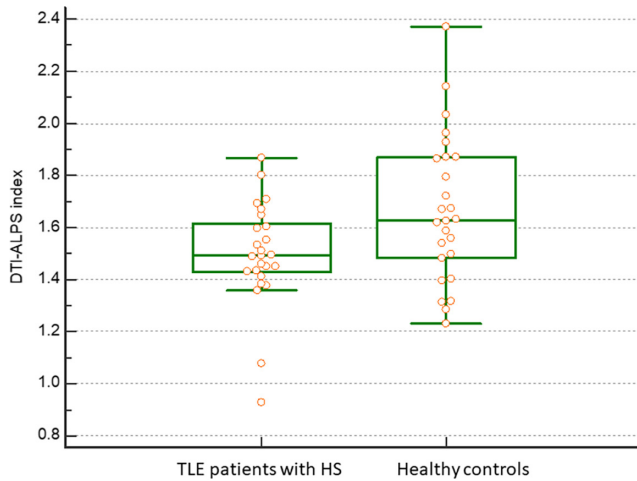
FIGURE 2 Differences in the DTI-ALPS index between TLE patients with HS and healthy controls. This figure shows that the DTI-ALPS index in TLE patients with HS was significantly lower than that in healthy controls. DTI-ALPS index, diffusion tensor imaging analysis-along the perivascular space index; TLE, temporal lobe epilepsy; HS, hippocampal sclerosis
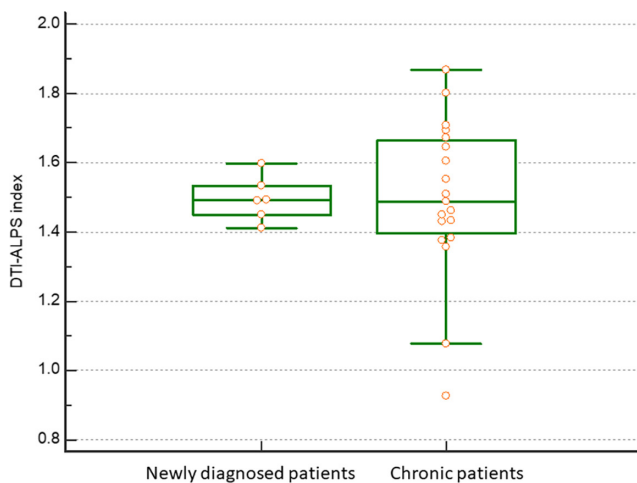

FIGURE 3 Differences in the DTI-ALPS index between newly diagnosed TLE patients with HS and chronic TLE patients with HS. This figure reveals that there is no significant difference in the DTI-ALPS index between the newly diagnosed TLE patients with HS and the chronic TLE patients with HS. DTI-ALPS index, diffusion tensor imaging analysis-along the perivascular space index; TLE, temporal lobe epilepsy; HS, hippocampal sclerosis

suggest the possible use of a new biomarker to monitor glymphatic function of patients with neurological disorders in a non-invasive manner.

In our previous study on epilepsy, we first demonstrated that there was a significant glymphatic system dysfunction in patients with juvenile myoclonic epilepsy using the DTI-ALPS method.[31] Juvenile myoclonic epilepsy is one of the most common types of genetic generalized epilepsy, and TLE with HS is focal epilepsy.

Therefore, glymphatic system dysfunction is probably not limited to TLE with HS but is likely to occur in all patients with epilepsy. Previous research demonstrated widespread alterations of cortical thickness and subcortical volumes, as well as cerebral white matter in patients with epilepsy.[32–34] In addition, the altered patterns were different across epilepsy syndromes.[32–34] Analysis of post-mortem brain tissue from epileptic patients confirmed an increased number of activated microglia, and elevated fractions of microglia were different according to cortical thickness.[35] Therefore, we could assume that the glymphatic system function is different across epilepsy syndromes because glymphatic system consists of glial cells. Further studies are needed to investigate the differences of glymphatic system function according to epilepsy types.

In this study, the DTI-ALPS index showed a significant negative correlation with age in patients with epilepsy, as well as healthy controls, but there was no correlation with other clinical factors of epilepsy. The function of the glymphatic system is impaired in the aging brain.[24] Loss of perivascular aquaporin-4 polarization and the reduction of cerebral arterial pulsatility have been identified as major causes of glymphatic system dysfunction associated with aging. Impaired distribution of growth factors, neuromodulators, carrier proteins, and other solutes due to glymphatic system dysfunction according to natural aging are exacerbated by the aggregation of misfolded proteins in several neurodegenerative disorders, resulting in cognitive decline.[24] As mentioned above, the effect of seizures on the glymphatic system may be related to the alteration in distribution and clearance of ASM in the brain parenchyma.[20,26] Thus, we initially hypothesized that there would be a difference in the DTI-ALPS index according to the duration of epilepsy or the number of ASMs associated with seizure burden, among clinical factors; however, the DTI-ALPS index did not significantly correlate with these clinical factors.

This is the first study to evaluate glymphatic system function in TLE patients with HS. Although we successfully demonstrated glymphatic system dysfunction in TLE patients with HS, this study has some limitations. First, the sample size was relatively small, and the study was conducted at a single center. However, we only enrolled TLE patients with HS to increase the sample homogeneity of epilepsy. Second, we could not exclude the effects of ASM on glymphatic system function, and the present results originated from ASM rather than epilepsy itself. However, we found that there were no differences in the DTI-ALPS index between newly diagnosed TLE patients with HS and chronic TLE patients with HS. In addition, there was no correlation between the number of ASM

and the DTI-ALPS index. Third, we could not control the time of MRI due to the retrospective study design. The glymphatic system function is activated during sleep, especially during sleep stage N3, whereas it is deactivated during daytime.[36] However, we accessed the glymphatic system function using the DTI-APLS index, which was based on structural MRI and DTI. Thus, the effects of time of MRI may not be a critical factor for evaluating glymphatic system dysfunction in TLE patients with HS. Fourth, we manually drew the ROIs and obtained the diffusivity along the axis at the three fibers, which could have resulted in variations across measurements. However, we initially identified each fiber with a different color of DTI. Moreover, we obtained the fiber orientation and diffusivity at the ROI at the voxel level and finally selected one voxel for each fiber with maximum orientation on the same x-axis, which could elevate the accuracy for finding each fiber. In addition, a recent study successfully demonstrated good test–retest reproducibility of the DTI-ALPS method.[37] Lastly, although we drew a ROI in the contralateral side of HS in order to exclude the effects of HS on the diffusivities in the fibers, we could not eliminate the possibility of affecting the value of diffusivity. Research on the effects of lesion, including HS, on the access of glymphatic system functions by the DTI-ALPS method has not been conducted, so it is judged that future research on this issue should be conducted. Further studies are needed to confirm these findings.

5 | CONCLUSION

Our findings showed that the DTI-ALPS index was significantly lower in TLE patients with HS than in healthy controls, indicating the presence of glymphatic system dysfunction. Our study also suggests that the DTI-ALPS index may be useful for evaluating glymphatic system function in epilepsy.

CONFLICTS OF INTEREST
None of the authors has any conflict of interest to disclose.

ETHICAL APPROVAL
We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES

1. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol. 2018;17(11):1016–24.
2. Mestre H, Mori Y, Nedergaard M. The Brain's Glymphatic system: current controversies. Trends Neurosci. 2020;43(7):458–66. https://doi.org/10.1016/j.tins.2020.04.003
3. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The Glymphatic system: A beginner's guide. Neurochem Res. 2015;40(12):2583–99. https://doi.org/10.1007/s11064-015-1581-6
4. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates csf flow through the brain parenchyma and the clearance of interstitial solutes, including Amyloid β. Sci Transl Med. 2012;4(147):111–47. https://doi.org/10.1126/scitranslmed.3003748
5. Mestre H, Tithof J, Du T, Song W, Peng W, Sweeney AM, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat Commun. 2018;9(1):1–9. https://doi.org/10.1038/s41467-018-07318-3
6. Lee H, Mortensen K, Sanggaard S, Koch P, Brunner H, Quistorff B, et al. Quantitative Gd-DOTA uptake from cerebrospinal fluid into rat brain using 3D VFA-SPGR at 9.4T. Magn Reson Med. 2018;79(3):1568–78. https://doi.org/10.1002/mrm.26779
7. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. J Clin Investig. 2013;123(3):1299–309. https://doi.org/10.1172/JCI67677
8. Ringstad G, Vatnehol SAS, Eide PK. Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain. 2017;140(10):2691–705. https://doi.org/10.1093/brain/awx191
9. De Leon MJ, Li Y, Okamura N, Tsui WH, Saint-Louis LA, Glodzik L, et al. Cerebrospinal fluid clearance in Alzheimer disease measured with dynamic PET. J Nucl Med. 2017;58(9):1471–6. https://doi.org/10.2967/jnumed.116.187211
10. Kiviniemi V, Wang X, Korhonen V, Keinänen T, Tuovinen T, Autio J, et al. Ultra-fast magnetic resonance encephalography of physiological brain activity–glymphatic pulsation mechanisms? J Cereb Blood Flow Metab. 2016;36:1033–45.
11. Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, et al. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Japan J Radiol. 2017;35(4):172–8. https://doi.org/10.1007/s11604-017-0617-z
12. Taoka T, Ito R, Nakamichi R, Kamagata K, Sakai M, Kawai H, et al. Reproducibility of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating interstitial fluid diffusivity and glymphatic function: CHanges in Alps index on Multiple conditiON acquIsition eXperiment (CHAMONIX) study. Japan J Radiol. 2022;40(2):147–58. https://doi.org/10.1007/s11604-021-01187-5
13. Zhang W, Zhou Y, Wang J, Gong X, Chen Z, Zhang X, et al. Glymphatic clearance function in patients with cerebral small

vessel disease. NeuroImage. 2021;238:118257. https://doi.org/10.1016/j.neuroimage.2021.118257

14. Bae YJ, Choi BS, Kim J-M, Choi J-H, Cho SJ, Kim JH. Altered glymphatic system in idiopathic normal pressure hydrocephalus. Parkinsonism Relat Disord. 2021;82:56–60. https://doi.org/10.1016/j.parkreldis.2020.11.009

15. Téllez-Zenteno JF, Hernández-Ronquillo L. A review of the epidemiology of temporal lobe epilepsy. Epilepsy Res Treat. 2012;2012:1–5. https://doi.org/10.1155/2012/630853

16. Blümcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: A Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia. 2013;54(7):1315–29. https://doi.org/10.1111/epi.12220

17. Rabinovitch A, Aviram I, Biton Y, Braunstein D. Explaining recent postictal epilepsy EEG results by the G-lymphatic clearance hypothesis. Med. Hypotheses. 2020;137:109600. https://doi.org/10.1016/j.mehy.2020.109600

18. Gorter JA, van Vliet EA, Aronica E. Status epilepticus, blood–brain barrier disruption, inflammation, and epileptogenesis. Epilepsy Behav. 2015;49:13–6.

19. Liu C, Habib T, Salimeen M, Pradhan A, Singh M, Wang M, et al. Quantification of visible Virchow–Robin spaces for detecting the functional status of the glymphatic system in children with newly diagnosed idiopathic generalized epilepsy. Seizure. 2020;78:12–7. https://doi.org/10.1016/j.seizure.2020.02.015

20. Marchi N, Banjara M, Janigro D. Blood–brain barrier, bulk flow, and interstitial clearance in epilepsy. J Neurosci Methods. 2016;260:118–24.

21. Janigro D. Are you in or out? Leukocyte, ion, and neurotransmitter permeability across the epileptic blood–brain barrier. Epilepsia. 2012;53:26–34.

22. Dadas A, Washington J, Janigro D. Cerebral waste accumulation and glymphatic clearance as mechanisms of human neurological diseases. J Neurol Neuromed. 2016;1(7):15–9. https://doi.org/10.29245/2572.942X/2016/7.1082

23. Lee HJ, Lee DA, Shin KJ, Park KM. Glymphatic system dysfunction in patients with juvenile myoclonic epilepsy. J Neurol. 2022;269:2133–2139. https://doi.org/10.1007/s00415-021-10799-w

24. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, et al. Impairment of paravascular clearance pathways in the aging brain. Ann Neurol. 2014;76(6):845–61. https://doi.org/10.1002/ana.24271

25. Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, et al. Biomarkers of traumatic injury are transported from brain to blood via the Glymphatic system. J Neurosci. 2015;35(2):518–26. https://doi.org/10.1523/JNEUROSCI.3742-14.2015

26. de Vries HE, Kooij G, Frenkel D, Georgopoulos S, Monsonego A, Janigro D. Inflammatory events at blood–brain barrier in neuroinflammatory and neurodegenerative disorders: implications for clinical disease. Epilepsia. 2012;53:45–52.

27. Puvenna V, Engeler M, Banjara M, Brennan C, Schreiber P, Dadas A, et al. Is phosphorylated tau unique to chronic traumatic encephalopathy? Phosphorylated tau in epileptic brain and chronic traumatic encephalopathy. Brain Res. 2016;1630:225–40.

28. Rabinovitch A, Aviramd I, Biton Y, Braunstein D. A combined astrocyte – G-lymphatic model of epilepsy initiation, maintenance and termination. Med Hypotheses. 2019;133:109384. https://doi.org/10.1016/j.mehy.2019.109384

29. McKnight CD, Trujillo P, Lopez AM, Petersen K, Considine C, Lin Y-C, et al. Diffusion along perivascular spaces reveals evidence supportive of glymphatic function impairment in Parkinson disease. Parkinsonism Relat Disord. 2021;89:98–104. https://doi.org/10.1016/j.parkreldis.2021.06.004

30. Chen H-L, Chen P-C, Lu C-H, Tsai N-W, Yu C-C, Chou K-H, et al. Associations among cognitive functions, plasma DNA, and Diffusion Tensor Image along the Perivascular Space (DTI-ALPS) in patients with Parkinson's disease. Oxidat Med Cell Long. 2021;2021:1–10. https://doi.org/10.1155/2021/4034509

31. Lee H-J, Lee DA, Shin KJ, Park KM. Glymphatic system dysfunction in patients with juvenile myoclonic epilepsy. J Neurol. 2021;1–7. https://doi.org/10.1007/s00415-021-10799-w

32. Whelan CD, Altmann A, Botia JA, Jahanshad N, Hibar DP, Absil J, et al. Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. Brain. 2018;141(2):391–408. https://doi.org/10.1093/brain/awx341

33. Hatton SN, Huynh KH, Bonilha L, Abela E, Alhusaini S, Altmann A, et al. White matter abnormalities across different epilepsy syndrome in adults: an ENIGMA-Epilepsy study. Brain. 2020;143:2454–73.

34. Lariviere S, Rodriguez-cruces R, Royer J, Caligiuri ME, Gambardell A, Conch L, et al. Network-based atrophy modeling in the common epilepsies: A worldwide ENIGMA study. Sci Adv. 2020;6(47):eabc6457.

35. Altmann A, Ryten M, Nunzi MD, Ravizz T, Tolomeo D, Reynold RH, et al. A systems-level analysis highlights microglial activation as a modifying factor in common epilepsies. Neuropathol Appl Neurobiol. 2022;48(1):e12758.

36. Mendelsohn AR, Larrick JW. Sleep facilitates clearance of metabolites from the brain: Glymphatic function in aging and neurodegenerative diseases. Rejuven Res. 2013;16(6):518–23. https://doi.org/10.1089/rej.2013.1530

37. Taoka T, Ito R, Nakamichi R, Kamagata K, Sakai M, Kawai H, et al. Reproducibility of diffusion tensor image analysis along the perivascular space (DTI-ALPS) for evaluating interstitial fluid diffusivity and glymphatic function: CHanges in Alps index on Multiple conditiON acquIsition eXperiment (CHAMONIX) study. Japan J Radiol. 2022;40(2):147–58. https://doi.org/10.1007/s11604-021-01187-5

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