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ORIGINAL RESEARCH

Glymphatic System Dysfunction in Elderly Patients with Late-Onset Epilepsy and Comorbid Chronic Insomnia Revealed by Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS)

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Purpose: This study assessed the influence of glymphatic system (GS) dysfunction on cognitive decline in patients with late-onset epilepsy (LOE) and comorbid chronic insomnia utilizing diffusion tensor imaging along the perivascular space (DTI-ALPS).

Methods: Clinical data were collected from 42 elderly LOE patients, 17 with and 25 without chronic insomnia, as well as from 22 healthy controls (HCs) matched for age and sex. Simoa assays were performed to quantify Aβ42 and Aβ40 as plasma biomarkers of age-related neuropathology, and associations between the DTI-ALPS index and age, seizure frequency and duration, Sleep Quality Index (PSQI), Hamilton Rating Scale for Depression (HAMD), Hamilton Rating Scale for Anxiety (HAMA), Mini-Mental State Examination (MMSE), and Aβ42:Aβ40 ratio (Aβ42/40) were assessed using Spearman correlation tests and multivariate logistic regression models.

Results: Both DTI-ALPS index and Aβ42/40 were significantly lower among LOE patients compared to HCs, and post-hoc analysis revealed even lower Aβ42/40 and DTI-ALPS index values among LOE patients with comorbid chronic insomnia compared to HCs and LOE patients without chronic insomnia. The DTI-ALPS index was negatively correlated with age, disease duration, PSQI score, and HAMA score, and positively correlated with Aβ42/40 and MMSE score among LOE patients according to Spearman's tests. Multivariate linear regression revealed independent associations of the DTI-ALPS index with age, MMSE score, Aβ42/40, and PSQI after adjusting for vascular risk factors, sex, and education.

Conclusion: These results suggest that the GS is dysfunctional in LOE and may exacerbate sleep disruption and cognitive impairments.

Keywords: glymphatic system, late-onset epilepsy, chronic insomnia, cognitive function, DTI-ALPS

Introduction

Epilepsy incidence rises significantly during late adulthood, peaking among individuals over 50 years of age at nearly double that of young adults.[1] The majority of elderly individuals diagnosed with late-onset epilepsy (LOE) exhibit risk factors for seizures such as neurovascular trauma, tumor, encephalitis, or other brain injuries,[2] but over one quarter of LOE cases remain without an identifiable etiology despite extensive diagnostic evaluations, termed late-onset epilepsy of unknown etiology (LOEU).[3] Recent studies have demonstrated that LOE is independently associated with cognitive decline and increased risk of dementia, particularly Alzheimer's disease (AD).[4] According to epidemiological data, roughly 30% of LOEU patients with active seizures exhibit deposition of amyloid-β (Aβ) and hyperphosphorylated Tau

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protein, the core neuropathological signs of AD.[5] Consequently, it is now acknowledged that LOEU may be a prodromal phase of AD. These findings suggest a potential chain effect wherein amyloidosis acts as a critical intermediary in the bidirectional exacerbation of LOE and AD.

Chronic insomnia is defined as difficulty falling asleep, maintaining sleep, and (or) awakening early in the morning, and often leads to fatigue, attention deficits, and emotional instability during the daytime.[6] Sleep disturbances, including chronic insomnia, are highly prevalent among patients with LOE.[7] Seizures alone can reduce sleep efficiency and total sleep duration while exacerbating sleep fragmentation,[8] and this chronic insomnia or sleep deprivation may in turn worsen seizure control.[9] Moreover, both epileptic activity and chronic insomnia accelerate brain Aβ plaque deposition,[10] suggesting that LOEU and chronic insomnia can act synergistically to accelerate age-related neurodegeneration and cognitive decline.

The glymphatic system (GS) is the primary clearance pathway for metabolic waste products in the central nervous system (CNS) and so is implicated in numerous disorders associated with the accumulation of neurotoxic byproducts such as AD and epilepsy.[11,12] The clearance of waste products by the GS is mediated by glial cells expressing aquaporin-4 (AQP-4) water channels that direct the flow of cerebrospinal fluid (CSF) from the arterial perivascular space to the interstitial compartment and subsequently into surrounding veins, deep cervical lymphatic vessels, and meningeal lymphatic vessels, providing a bulk-flow pathway for movement of metabolic waste from the interstitium to the systemic circulation.[13] Animal experiments have demonstrated that impaired GS function results in the accumulation of Aβ and tau proteins within the CNS parenchyma,[14] suggesting that GS dysfunction may link LOE, chronic insomnia, and cognitive impairment. Notably, preclinical intervention studies have demonstrated that accelerating GS clearance can reduce epileptic discharge frequency and improve cognitive performance.[15]

Extending these findings to humans requires a non-invasive and safe method for the assessment of GS function. Taoka et al[16] introduced diffusion tensor image analysis along the perivascular space (DTI-ALPS) as a novel method to assess the efficiency of GS function in clinical studies.[17,18] The DTI-ALPS index measures water molecule movement within the perivascular space (PVS) by quantifying diffusivity[19] and is based on the premise that the PVS is predominantly oriented orthogonally to white matter association and projection tracts located near the body of the lateral ventricle.[19] The DTI-ALPS index is then calculated based on the diffusion coefficients of projection fibers along the x-axis (Dxxproj) plus association fibers along the x-axis (Dxxassoc), and is further refined by incorporating the diffusion coefficients of association fibers along the z-axis and well as projection fibers along the y-axis.[19] Consequently, a lower DTI-ALPS index value signifies reduced PVS diffusivity, which may in turn indicate GS dysfunction. This method eliminates the need for tracer injection while still demonstrating strong intergroup consistency.

However, despite numerous studies on the contributions of the GS to diverse age-related neurodegenerative diseases,[20,21] there is limited research on the associations of GS function with LOE and comorbidities. Furthermore, the plasma Aβ42: Aβ40 concentration ratio (Aβ42/40), a biomarker of brain amyloid plaque load and AD risk, may also indicate elevated LOE risk.[22] Therefore, the current retrospective study investigated the potential contributions of GS dysfunction to LOE with comorbid chronic insomnia by evaluating associations of the DTI-ALPS index with various clinical markers and age-associated cognitive decline.

Methods

Participants

Associations among epilepsy, the DTI-ALPS index, sleep quality, plasma Aβ42/40, and cognitive deficits were assessed by retrospectively reviewing the clinical findings of LOE patients (n = 42) enrolled from our hospital's epilepsy center from January 2022 to October 2024. Selection criteria for newly diagnosed LOE with or without chronic insomnia were as follows: (1) age 50 years old and older; (2) meeting 2017 ILAE diagnostic criteria for LOE;[23] (3) chronic insomnia compliant according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5);[24] (4) no evident responsible lesions for epilepsy (eg, tumors, cortical or lobar injuries) identified upon visual evaluation of routine 3.0-T brain magnetic resonance imaging (MRI) scans; (5) DTI data of sufficient quality for quantitative analysis; (6) no systemic or mental illnesses; (7) clinical data including cognitive, sleep, and neuropsychological assessments. In addition, healthy

controls (HCs, n = 22) matched for sex ratio and age distribution and demonstrating no evidence of severe structural lesions on brain 3.0-T MRI scans were enrolled from the hospitalization database. All participants were right-handed.

Clinical Evaluations

General cognitive function was assessed using the Chinese version of the Mini-Mental State Examination (MMSE),[25] while anxiety was assessed using the Hamilton Anxiety Scale (HAMA), insomnia by the Pittsburgh Sleep Quality Index (PSQI), and depression using the Hamilton Depression Scale (HAMD).

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Quantification of Plasma Aβ42/Aβ40 Concentrations

Peripheral blood samples were collected from all participants in anticoagulant tubes the morning after an overnight fast and centrifuged for 10 min at 4000 g to isolate plasma. Plasma samples was stored at −80°C until analysis. Concentrations of $A\beta_{42}$ and $A\beta_{40}$ were measured using digital immunoassay technology (Simoa) on an HD-X analyzer (Quanterix Corp., Billerica, MA, USA). Plasma samples were diluted fourfold as per the manufacturer's protocol for the Human Neuro 3-Plex A kit (Quanterix, #101995).

MRI Acquisition and Processing

Diffusion tensor images were acquired from all participants using a 3.0-T MRI scanner (GE Healthcare) equipped with a 32-channel head coil. Images were obtained by a single echo planar imaging (EPI) sequence of the following parameters: 32 diffusion-weighted directions; *b*-values of 0 and 1000 s/mm^2; flip angle of 90°; repetition time (TR) = 8620 ms; matrix size, 120 × 120; echo time (TE) = 85 ms; slice thickness of 2.25 mm; field of view (FOV) of 240×240 mm^2; interslice gap of 1 mm.

Images data were processed using the 2021 version of DSI Studio Software (available at http://dsi-studio.labsolver.org). The DTI-ALPS index was calculated using established protocols (Figure 1). Briefly, the processing pipeline encompassed opening source images, correcting for vortex and phase distortion artifacts, determining processing parameters (smoothing, thresholds, defragmentation, etc.), recreating the DTI data, and fiber tracking. The left hemisphere projection fibers (Dxxproj) and association fibers (Dxxassoc) at the lateral ventricle body level were selected to define 5-mm diameter regions of interest (ROIs). Subsequently, fiber orientations and diffusivities were extracted from the ROIs along the x-, y-, and z-axes at the voxel level. The ROIs with the highest directional coherence were selected for each fiber type (projection, subcortical fibers, association, etc.) based on the same diffusivity along the x-axis. The DTI-ALPS index was then computed according to the formula,

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

where the numerators Dxxproj and Dxxassoci are the diffusivities of the projection and association fibers along the x-axis, and the denominators Dyyproj and Dzzassoc are the diffusivities of the projection fibers along the y-axis and association fibers along the z-axis, respectively.

Statistical Analysis

Group differences in categorical variables were evaluated by chi-squared tests, while group differences in continuous variables were evaluated by analysis of variance (ANOVA). Associations between the DTI-ALPS index and clinical parameters (age, PSQI, scores of MMSE, HAMA and HAMD, Aβ42/40, and frequency and duration of seizures) were evaluated by calculating Spearman correlation coefficients. Diffusivities along fiber axes were corrected for multiple

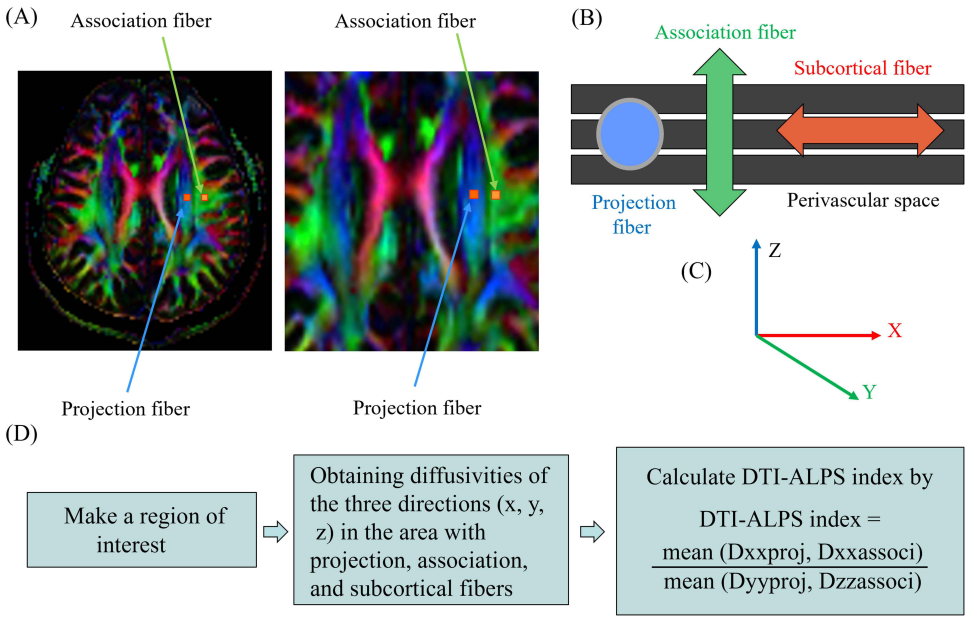

Figure 1 The process for obtaining DTI analysis along the perivascular space index. (**A**) Place the region of interests in the areas with projection and association fibers. (**B**) The direction of the paravascular space (gray columns) and the orientation of the three neural fiber tracts. (**C**) The directions of the projection fiber tracts (blue; z-axis), association fibers tracts (green, Y-axis), and subcortical fibers tracts (red, X-axis). (**D**) Flowchart illustrating the process of calculating DTI-ALPS index.

comparisons using the Bonferroni method (P =0.05/9 =0.0055). Independent risk factors associated with the DTI-ALPS index were identified by linear regression models. MedCalc® Statistical Software (version 20) and GraphPad Prism (version 7) were employed for statistical analyses and mapping, respectively. A $P < 0.05$ (two-tailed) was considered statistically significant for all tests.

Results

Clinical Characteristics of Participants

The LOE group (n = 42) included 25 patients without chronic insomnia and 17 patients with chronic insomnia. Average age, sex ratio, mean years of education, and cerebrovascular risk factors did not differ significantly among LOE patient subgroups and HCs (Table 1). As expected, PSQI scores were significantly higher among LOE patients with chronic insomnia than patients without chronic insomnia and HCs ($P < 0.05$). In addition, both HAMD and HAMA scores were higher, while MMSE scores were lower in the comorbid LOE subgroup ($P < 0.05$). Thus, the comorbid subgroup exhibited more severe symptoms of depression, anxiety, and cognitive decline. Moreover, both the frequency and duration of seizures were higher in the chronic insomnia subgroup ($P < 0.05$). However, antiseizure medication load did not differ between LOE subgroups ($P > 0.05$). The Aβ42/40 was lower in the chronic insomnia subgroup compared to LOE patients with normal sleep, suggest that comorbid patients were at higher risk of AD.

Comparative Analysis of Diffusivities and the DTI-ALPS Index

Table 2 summarizes the fiber diffusion coefficients along the x-, y-, and z-axes as well as the DTI-ALPS indices for all groups. Dxxproj was significantly lower in LOE patients than HCs while Dxxassoc, Dyyassoc, and Dzzproj did not differ among groups. The DTI-ALPS index was significantly lower in LOE patients than HCs. Additionally, the DTI-ALPS index was lower among comorbid LOE patients than LOE patients without comorbid chronic insomnia.

Correlation Analysis

There was a significant negative correlation between the DTI-ALPS index and age for the entire participant cohort ($r = -0.700$, $P < 0.001$, Figure 2A). In the total LOE patient group, there were significant positive correlations between DTI-ALPS index and both Aβ42/40 ($r=0.752$, $P < 0.001$, Figure 2B) and MMSE score ($r = 0.803$, $P < 0.001$, Figure 2C).

Table 1 Demographic and Clinical Characteristics of LOE Patients and Healthy Controls

	LOE (n=42)		HCs (n=22)	*P*-value	*P1*-value	*P2*-value	*P3*-value
	LOE with Chronic Insomnia (n=17)	LOE without Chronic Insomnia (n=25)					
Demographic characteristics							
Age, y, mean (SD)	65.6 (6.8)	62.2 (9.3)	64.7 (9.1)	0.425	0.224	0.747	0.339
Female sex, n (%)	7 (41.2)	6 (24.0)	8 (36.4%)	0.462	–	–	–
Right handedness, n (%)	17 (100%)	25 (100%)	22 (100%)	1.0	–	–	–
Seizure characteristics							
Age at onset, y, mean (SD)	61.3 (6.1)	60.8 (7.8)	–	–	0.807	–	–
Seizure frequency, n/y, median (IQR)	4 (3, 5)	2 (2, 4)	–	**–**	**0.019**	**–**	**–**
Disease duration, m, median (IQR)	29 (11, 85)	8 (4.5, 32)	–	**–**	**0.004**	**–**	
ASMs load, n, M (IQR)	1 (1, 2)	1 (1, 1)	–	–	0.087	–	
Medical history							
Hypertension, n (%)	7 (41.2%)	8 (32.0%)	6 (27.3%)	0.653	–	–	–
Diabetes mellitus, n (%)	3 (17.6%)	4(16.0%)	3 (13.6%)	0.941	–	–	–
Coronary heart disease, n (%)	2 (11.8%)	1 (4.0%)	1 (4.5%)	0.547	–	–	–
Personal history							
Smoking, n (%)	6 (35.3%)	8 (32.0%)	5 (22.7%)	0.660	–	–	–
Drinking, n (%)	2 (11.8%)	6 (24.0%)	2 (9.1%)	0.327	–	–	–
Education, y, median (IQR)	3 (2.5, 6.5)	6 (3, 7.5)	5.5 (3, 7.3)	0.249	0.130	0.214	0.791
Neuropsychological assessments							
PSQI scores, median (IQR)	8 (7, 10)	3 (1.5, 4)	1 (0.75, 2)	**<0.001**	**<0.001**	**<0.001**	**0.012**
MMSE scores, mean (SD)	19.0 (2.6)	21.9 (3.8)	25.5 (3.1)	**<0.001**	**0.007**	**<0.001**	**0.001**
HAMD scores, median (IQR)	4 (3, 5)	3 (2, 4)	2 (1, 2)	**0.001**	**0.048**	**<0.001**	**0.032**
HAMA scores, median (IQR)	7 (6, 9)	4 (3, 6)	3 (2, 4)	**<0.001**	**<0.001**	**<0.001**	**0.036**
Plasma Aβ detection							
Aβ42, mean (SD), pg/mL	5.3 (0.69)	6.1 (1.0)	8.5 (1.1)	**<0.001**	**0.012**	**<0.001**	**<0.001**
Aβ40, mean (SD), pg/mL	118.9 (7.1)	121.9 (7.5)	128.1 (6.3)	**<0.001**	0.186	**<0.001**	**0.004**
Aβ42/40, mean (SD)	0.045 (0.007)	0.050 (0.007)	0.066 (0.006)	**<0.001**	**0.017**	**<0.001**	**<0.001**

Notes: Bold indicates p<0.05; Aβ, amyloid beta.
Abbreviations: LOE, late-onset epilepsy; HCs, healthy controls; ALPS, analysis along the perivascular space; PSQI, Pittsburgh Sleep Quality Index; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination.

There were also significant negative correlations between DTI-ALPS index and disease duration ($r = -0.026$, $P < 0.001$, Figure 2D), HAMA score ($r = -0.725$, $P < 0.001$, Figure 2E), and PSQI score ($r = -0.786$, $P < 0.001$, Figure 2F).

Linear regression model 1 controlling for education level and sex identified a significant independent association between DTI-ALPS and age ($\beta = -0.751$, $P < 0.001$) (Table 3). Model 2 controlling for neuropsychological scores and both frequency and duration of seizures revealed significant independent associations between DTI-ALPS index and age

Table 2 Comparison of the Diffusivities Among LOE Patients and HCs

Diffusivity	LOE (n=42)		HCs (n=22)	*P*-value	*P1*-value	*P2*-value	*P3*-value
	LOE with Chronic Insomnia (n=17)	LOE Without Chronic Insomnia (n=25)					
Dxxproj	0.00050±0.00006	0.00051±0.00005	0.00054±0.00004	**0.031**	0.520	**0.014**	**0.041**
Dxxassoc	0.00049±0.00004	0.00047±0.00006	0.00047±0.00005	0.317	0.182	0.176	0.952
Dyyproj	0.00050±0.00003	0.00050±0.00004	0.00048±0.00003	0.072	0.590	0.127	0.051
Dyyassoc	0.00111±0.00051	0.00109±0.00068	0.00113±0.00044	0.160	0.331	0.428	0.057
Dzzproj	0.00112±0.00005	0.00110±0.00007	0.00111±0.00006	0.853	0.575	0.717	0.839
Dzzassoc	0.00039±0.00006	0.00036±0.00004	0.0005±0.00007	0.321	0.787	0.292	0.148
ALPS index	1.22±0.09	1.33±0.14	1.40±0.11	**<0.001**	**0.005**	**<0.001**	0.065

Notes: Data are represented as Mean ± SD. Bold indicates $p<0.05$.

Abbreviations: ALPS, analysis along the perivascular space; Dxxassoc, diffusivity along the x-axis in the association fiber; Dxxproj, diffusivity along the x-axis in the projection fiber; Dyyassoc, diffusivity along the y-axis in the association fiber; Dyyproj, diffusivity along the y-axis in the projection fiber; Dzzassoc, diffusivity along the z-axis in the association fiber; Dzzproj, diffusivity along the z-axis in the projection fiber; LOE, late-onset epilepsy; HCs, healthy controls.

($\beta = -0.139$, P = 0.015), Aβ42/40 ($\beta = 0.238$, P = 0.014), MMSE ($\beta = 0.222$, P = 0.010), and PSQI score ($\beta = -0.192$, P = 0.020), and these associations remained significant in linear regression model 3 adjusted for cerebrovascular risk factors (age, $\beta = -0.109$ and P = 0.039; Aβ42/40, $\beta = 0.294$ and P = 0.035; MMSE, $\beta = 0.273$ and P = 0.025; PSQI, $\beta = -0.338$ and P = 0.043).

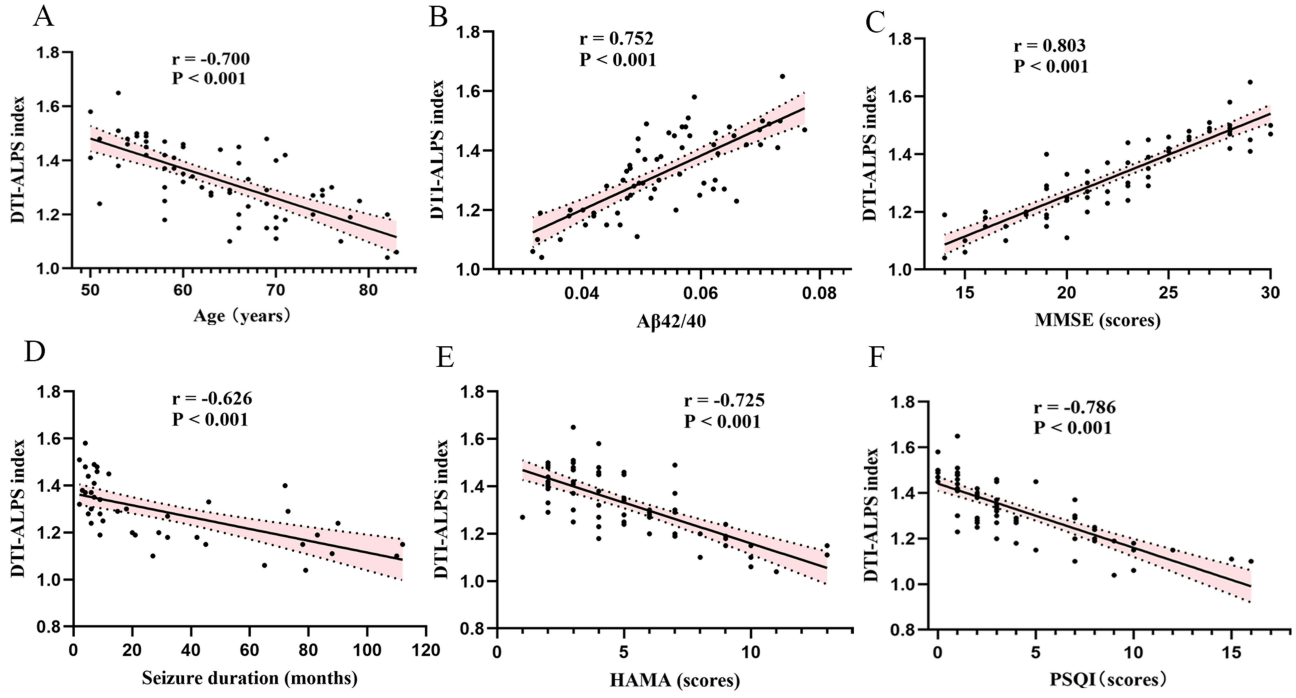

Figure 2 Linear correlation between DTI-Alps index and clinical indicators. (**A**) Negative correlation between the DTI-ALPS index and ages in all participants. (**B**) Positive correlation between the DTI-ALPS index and Aβ42/40 in LOE patients. (**C**) Positive correlation between DTI-ALPS index and MMSE scores in LOE patients. (**D**) Negative correlation between DTI-ALPS index and seizure duration in LOE patients. (**E**) Negative correlation between the DTI-ALPS index and HAMA scores. (**F**) Negative correlation between the DTI-ALPS index and PSQI scores.

Table 3 The Multivariable Linear Regression for the DTI-ALPS Index in LOE Patients

	Model 1		Model 2		Model 3	
	β	*P* value	*β*	*P* value	*β*	*P* value
Age	−0.751	**<0.001**	−0.139	**0.015**	−0.109	**0.039**
Sex	0.079	0.456	0.023	0.782	0.032	0.566
Years of education	0.022	0.853	−0.067	0.143	−0.073	0.243
PSQI	–	–	−0.192	**0.020**	−0.338	**0.043**
HAMA	–	–	−0.086	0.360	−0.080	0.415
HAMD	–	–	−0.025	0.597	−0.029	0.541
MMSE	–	–	0.222	**0.010**	0.273	**0.025**
Aβ42/40	–	–	0.238	**0.014**	0.294	**0.035**
Seizure frequency	–	–	−0.181	0.148	−0.164	0.221
Disease duration	–	–	−0.138	0.056	−0.134	0.088
Hypertension	–	–	–	–	0.039	0.449
Diabetes mellitus	–	–	–	–	−0.010	0.855
Coronary heart disease	–	–	–	–	0.086	0.106
Smoking	–	–	–	–	−0.052	0.400
Drinking	–	–	–	–	0.044	0.478

Notes: Bold indicates $p<0.05$. Model 1: adjusted for age, sex, years of education; Model 2: adjusted for age, sex, years of education, PSQI, HAMA, HAMD, MMSE, Aβ42/40, seizure frequency, disease duration; Model 3: adjusted for age, sex, years of education, PSQI, HAMA, HAMD, MMSE, Aβ42/40, seizure frequency, disease duration; disease duration, hypertension, diabetes mellitus, coronary heart disease, smoking, drinking.

Abbreviations: DTI-ALPS, diffusion tensor imaging along the perivascular space; PSQI, Pittsburgh Sleep Quality Index; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; Aβ, amyloid beta.

Discussion

This study is the first to explore potential GS dysfunction in LOE complicated by chronic insomnia using the DTI-ALPS index. The DTI-ALPS index was significantly lower in LOE patients than HCs and even lower among patients with comorbid chronic insomnia, suggesting that sleep disruption among LOE patients may be associated with GS dysfunction. Additionally, a negative correlation was observed between the DTI-ALPS index and epilepsy duration, indicating a gradual deterioration in GS function during disease progression. Moreover, the DTI-ALPS index was negatively associated with age across all participants, implying that GS function diminishes with age even in the absence of overt pathology. While the DTI-ALPS index was not associated with depression or anxiety among LOE patients, a lower index was associated with greater plaque load as evidenced by the plasma Aβ42/40 ratio. Collectively, these findings suggest that GS dysfunction may ultimately enhance AD risk in LOE patients. Causal associations among DTI-ALPS index, epilepsy severity, insomnia, and AD risk warrant future study.

An age-related decline in GS activity is implicated in several neurodegenerative conditions, including AD.[26] Further, LOE patients are more susceptible to cognitive impairments than age-matched controls, suggesting that LOE may exacerbate the underlying neuropathology.[5,27] Increases in tau phosphorylation and Aβ deposition have been detected in LOE patients[28] and further implicated in epileptogenicity. Effective nighttime sleep enhances glymphatic clearance, thereby reducing pathological burden.[29] However, in LOE with comorbid chronic insomnia, the decline in sleep efficiency may reduce glymphatic clearance of metabolic waste products,[30] potentially worsening the neuropathologies underlying epileptogenesis and cognitive decline. Notably, pathogenic Aβ deposition may also disrupt the sleep–wake cycle,[31] thereby triggering a mutually reinforcing cycle of progressively worsening sleep disruption and Aβ deposition. Glymphatic system insufficiency may also contribute to epileptogenesis long before the deposition of insoluble Aβ.[32] Sleep disorders and abnormal electroencephalogram (EEG) activity are often among the earliest signs of dementia.[33] Additionally, recurrent epileptic seizures compromise the integrity of the blood-brain barrier (BBB), resulting in the accumulation of peripheral proinflammatory cytokines in the CNS and triggering potentially neurodegenerative

inflammation. Loss of BBB integrity also shifts the intracellular and extracellular ion concentrations in the CSF, contributing to cerebral edema.[34] Aquaporin-4 helps mitigate brain edema by facilitating CSF-interstitial fluid (ISF) exchange via GS flow, restoring ionic balance.[34,35] Downregulation of AQP-4 expression and ensuing disruption of ionic homeostasis following seizure activity may further compound GS dysfunction and increase AD risk. For instance, administration of the AQO-4 inhibitor TGN-20 to mice markedly diminished lymphatic CSF-ISF exchange and enhanced amyloid deposition,[36] suggesting that the AQP-4 protein as a promising therapeutic target for neurodegenerative conditions like LOE and AD.[37] In summary, age-associated reductions in CSF production, proinflammatory/anti-inflammatory imbalances, epileptiform seizure-induced brain edema, and diminished expression or localization of astrocytic AQP-4 may collectively disrupt CSF-ISF flow and reduce the efficiency of metabolic waste removal from the brain.

Extensive studies have corroborated DTI-ALPS detection technology as an effective tool for evaluating GS function. Among its advantages are high sensitivity to molecular micro-motion, non-invasive detection capabilities, and a relatively brief scanning time, making it particularly suitable for clinical application. Clinical investigations of epilepsy in particular, including focal epilepsy, refractory epilepsy, as well as status epilepticus (SE),[12,38] have revealed a strong association between a reduced DTI-ALPS index and impaired GS function. Notably, the DTI-ALPS index was reported to rise significantly in both ASM responders and postoperative patients receiving epilepsy surgery compared to pretreatment baseline.[39] Furthermore, Yu et al recently reported lower DTI-ALPS indices among elderly chronic insomnia patients, and even greater reductions among those exhibiting cognitive decline.[40] In fact, others have reported that shorter N2 sleep duration is both predictive of increased epileptic activity and an independent factor influencing DTI-ALPS decline.[41] However, no previous study had evaluated alterations in GS function among LOE patients with comorbid chronic insomnia. In the current study, the DTI-ALPS index was positively associated MMSE score (implying that lower DTI-ALPS predicts poorer cognition) and negatively associated with Aβ42/40 and PSQI scores (implying that lower DTI-ALPS predicts greater pathological load and poorer sleep). This study thus highlights the importance of cognitive assessment in studies of epilepsy. Moreover, the DTI-ALPS index was negatively correlated with epilepsy duration, implying that a longer disease course and more numerous epileptic seizures may progressively exacerbate GS impairment, that GS dysfunction results in epilepsy progression, or that both processes are mutually reinforcing. Based on these findings, we hypothesize that GS function acts as a crucial mechanism for mitigating cognitive decline and reducing the risk of AD in LOE patients. These findings strongly suggest that enhancing GS function may serve as a promising therapeutic approach for managing epilepsy and associated comorbidities.[42] In support of this notion, knockout of the Trpm4 gene and treatment with glibenclamide both promoted earlier recovery of GS function and brain edema following SE in mice, and these effects were accompanied by reduced phosphorylated tau protein accumulation and improved cognitive outcomes.[42]

This study has several limitations. First, the limited sample size and single-center retrospective design limit applicability to other clinical populations and preclude the investigation of other potentially significant associations. However, the same MRI scanner was utilized to maintain inter-data comparability. Second, some LOE patients may exhibit mild white matter lesions or brain atrophy undetectable by DTI that could nonetheless affect the DTI-ALPS index calculation. Third, it is possible that ASM may activate the GS, consequently influencing the DTI-ALPS index. Also, some ASMs can indirectly improve sleep, thereby reducing comorbid psychiatric disorders[43] as well as seizures. Therefore, the clinical value of ASMs for improving sleep in LOE patients requires further investigation. Fourth, the retrospective design and lack of follow-up preclude drawing definitive causal associations between GS dysfunction and cognitive decline in LOE patients. Last, other sleep disorder types such as obstructive sleep apnea (OSA), REM sleep behavior disorder, and parasomnia may be associated with GS dysfunction.[44] Given that our study only evaluated LOE comorbid with chronic insomnia, we cannot not rule out the potential confounding effects of these other sleep disorders.

Conclusions

Measurements of DTI-ALPS revealed weaker GS activity in LOE patients with chronic insomnia. Further, GS insufficiency was associated with more severe disease phenotype, greater AD risk, and cognitive decline, suggesting that the GS is a promising therapeutic target for age-related diseases.

Data Sharing Statement

The data generated and analyzed during the current study are not publicly accessible owing to patient privacy considerations but can be obtained from the corresponding author upon reasonable request.

Ethics Statement and Consent to Participate

The principles outlined in the 2013 revision of the Helsinki Declaration were strictly complied with in this study. The Ethics Committee of the Second People's Hospital of Hefei issued an approval for the research protocol. As the present study was retrospective, our Institutional Review Board waived the written informed consent. The data of the participants would be anonymized or kept confidential, without infringing upon any of their rights and interests.

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Disclosure

The authors report no conflicts of interest in this work.

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