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Glymphatic dysfunction in autoimmune encephalitis: A prospective assessment with MR DTI-ALPS index

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Abstract

Objective: This study aimed to evaluate glymphatic system function in patients with Autoimmune Encephalitis (AE) by utilizing the Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS) index, with the goal of exploring its relationship with clinical outcomes. *Methods:* Fifty three AE patients and 33 healthy controls (HCs) were enrolled and underwent 3T MRI examinations incorporating DTI sequences. To achieve this objective, the ALPS index, which derived by quantifying diffusivity within the perivascular spaces (PVS) surrounding the lateral ventricles, was computed. To evaluate disease progression, the modified Rankin Scale (mRS) was employed for severity assessment. Additional, relationships between the ALPS value, clinical evaluation results, and cerebrospinal fluid (CSF) indicators (including white blood cell count, total protein concentration) were explored through statistical analysis. *Results:* AE patients showed significantly lower ALPS indices compared to HCs (1.34 ± 0.12 vs. 1.43 ± 0.12, $p < 0.001$). A moderate negative correlation was observed between the ALPS index and mRS scores ($r = -0.66$, $p < 0.001$). Among anti-NMDAR encephalitis cases, the ALPS indices recorded were found to be the lowest at 1.28 ± 0.09. The ALPS index showed a weak inverse relationship with CSF protein levels ($r = -0.44$, $p = 0.013$) but not with CSF WBC count. Early immunotherapy responders demonstrated significant glymphatic functional recovery, corresponding to an increase in the ALPS index from 1.35 ± 0.13 to 1.41 ± 0.13 ($p < 0.001$).
Conclusion: The ALPS index shows great potential as a non-invasive biomarker for evaluating glymphatic system impairment, and it might also be useful for tracking how well patients respond to various therapeutic interventions in the context of AE. These results indicate that glymphatic system impairment could play a role in the disease process underlying AE.

Keywords: Autoimmune encephalitis, glymphatic system, DTI-ALPS, magnetic resonance imaging

INTRODUCTION

Autoimmune encephalitis (AE) is a collection of immune system-driven nervous system illnesses marked by inflammation in the brain tissue, usually triggered by antibodies that attack protein on or between nerve cells.[1] The symptoms of AE can vary widely, including problems with thinking, unusual behavior, fits, and movement issues, which can result in severe health problems and even death if not identified and treated quickly.[2,3] Although the main cause of AE involves antibodies interfering with normal nerve cell function and starting inflammatory processes, the exact ways the body removes harmful auto-antibodies and inflammatory substances from the brain are still not fully known.[4]

A pivotal advancement in neuroscience, the discovery of the glymphatic system has revolutionized our comprehension of how the brain rids itself of waste.[5] This system operates as a comprehensive network, facilitating the effective removal of metabolic byproducts and harmful substances via the Perivascular Space (PVS), which are lined by astrocytic endfeet containing high concentration of aquaporin-4 (AQP4) water channels.[6] Preserving the normal functioning of this waste-clearing pathway is crucial for the brain to maintain a stable internal environment;

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when it malfunctions, it is closely linked to the development of numerous neurological disorders, such as Alzheimer's disease and traumatic brain injury.[7,8] Importantly, emerging research suggests that in AE, neuroinflammatory processes, such as the improper positioning of AQP4, damage to the blood-brain barrier, and the infiltration of inflammatory cells into PVS.[9,10]

The Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS) technique emerges as a potential, non-invasive means for evaluating glymphatic function in living organisms, presenting a feasible method suitable for both scientific research and medical practices.[11] This creative method water diffusion along the PVS in the cerebral white matter, serving as an indirect indicator of glymphatic system function.[12] Although the DTI-ALPS index has proven effective in studying glymphatic impairment across different neurological disorders[13,14], its use in AE remains poorly explored.

To bridge this important gap in understanding, the current research aimed to examine glymphatic system functionality in patients with AE through a methodical assessment using the DTI-ALPS index. Previous research has indicated potential connections between glymphatic system activity and neurological conditions, and we aim to explore whether individuals with AE display notable disruptions in this system. Our expectation is that such disruptions would be quantifiable through the DTI-ALPS index and would show associations with both the severity of clinical symptoms and specific indicators of inflammation in the CSF. To achieve this, the current study aims to deepen comprehension of the pathological mechanism underlying AE and discover novel imaging-based indicators that can be used for tracking disease progression and assessing treatment efficacy.

METHODS

Study participants

From August 2023 through May 2025, the Third Affiliated Hospital of Sun Yat-sen University identified 53 patients who met the criteria for AE. To ensure the validity of the research, the enrollment criteria for these participants were set as follows: (1) age ranging from 17 to 70 years; (2) meeting the strict diagnostic standards for definite AE; (3) having comprehensive clinical and laboratory information available; and (4) being able to receive MRI assessments. In contrast, the research excluded participants based on specific restrictions. These included: (1) having other neurological conditions that might interfere with outcomes, such as neurodegenerative illnesses, cerebrovascular issues, or simultaneous central nervous system infections; (2) a history of severe systemic diseases that impact brain function; (3) being unsuitable for MRI procedures; and (4) image data of insufficient quality that made precise analysis impossible.

A control group consisting of 33 healthy individuals was selected, with age and gender matching to the AE patients, thereby ensuring the possibility of valid comparisons. HCs were free from any history of neurological or systemic infections, chronic illnesses, or conditions that might impair glymphatic function, allowing for valid comparison with patients suffering from AE and emphasizing potential differences in normal glymphatic system activity.

The research plan received formal approval from the Ethics Committee at the Third Affiliated Hospital of Sun Yat-sen University. In strict accordance with the ethical guidelines outlined in the Declaration of Helsinki, all individuals who participated in this research were selected through a rigorous process. Prior to enrollment, every individual was provided with a comprehensive explanation of the study's procedures, and upon confirming their comprehension, formal written consent was formally obtained from each of them.

Clinical evaluation

Every patient was subjected to a minimum of one magnetic resonance imaging (MRI) scan and dynamic electroencephalography (EEG) monitoring procedure. To assist in the diagnosis, testing for autoimmune antibodies was performed using semi-quantitative indirect immunofluorescence testing (IIFT) on serum and/or CSF samples. Baseline demographic details and the count of distinctive clinical manifestations for AE, such as convulsions, mental health disturbances, reduced awareness, motor function abnormalities, difficulty swallowing, autonomic nervous system imbalances, and cognitive function decline, were gathered. This assessment tool, known as the modified Rankin Scale (mRS), is ordinal scale that spans from 0 to 6, with higher numerical values indicating a more severe level of disability. To guarantee uniformity and dependability, all evaluations were separately assessed by two medical

doctors specializing in neurology. In addition, other clinical metrics collected involved the length of time symptoms had been present, CSF indicators such as WBC count and protein levels, as well as whether participants were currently undergoing immunotherapy. Table 1 provides a comprehensive overview of the clinical features of every enrolled subject.

MRI acquisition and DTI parameters

MRI examinations were carried out on a 3.0T medical imaging system (Signa Architect, GE Healthcare, USA) utilizing a 48-channel head coil for the procedure. Prior to contrast enhancement, DTI was implemented following a consistent protocol, with each participant undergoing the acquisition of two DTI datasets that shared the same sequence parameters. DTI parameters were as follows: FOV = 240mm x 240mm, TR/TE = 6500/85ms, b-values = 0, 1000 s/mm², 32 directions, 2 mm isotropic voxels, imaging matrix = 128 x 128, number of shot =3, acquisition number of slices =64, excitation times (NEX) = 4, acquisition time = 4 minutes and 36 seconds.

ALPS index calculation

The PVS is a vital component of the cerebral lymphatic - like drainage network, with water movement through this structure acting as an indicator of glymphatic system functionality. This connection is utilized at the region of the lateral ventricle. In this context, the orientation of the PVS and nearby medullary veins is perpendicular to the ventricular wall, with projection fibers running vertically relative to these structures. This particular structural configuration allows for the targeted examination of water molecule diffusion precisely along the PVS (Figure 1a).

Based on this anatomical principle, The DTI-ALPS index is computed. To compute the ALPS index15, diffusion tensor images in this research

Table 1: Demographic and clinical characteristics of the study population

Variables	AE n=53	HC n=33	*p*
Age (mean ± SD)	35.3 ± 14.7	38.8 ± 11.5	0.245
Sex			1.000
Male n (%)	31 (58.49)	13 (39.39)	
female n (%)	22 (41.51)	20 (60.61)	
Symptoms n (%)			
Seizure	35 (66.03)	/	/
Psychiatric symptom	40 (75.47)	/	/
Disorders of consciousness	33 (62.26)	/	/
Dysphasia	32 (60.37)	/	/
Movement disorder	38 (71.69)	/	/
Cognitive impairment	49 (92.45)	/	/
Autonomic dysfunction	36 (67.92)	/	/
Antibody type n (%)			
Anti-NMDAR	20 (37.73）	/	/
Anti-GABABR	9 (16.98)	/	/
Anti-LGI1	8 (15.09)	/	/
Anti-GFAP	16 (30.19)	/	/
CSF WBC count (10^6/L) [median (IQR)]	10 (4-37)	/	/
CSF protein (g/L) [mean ± SD]	0.39 ± 0.12	/	/
MRI abnormality n (%)	32 (60.37)	/	/
EEG abnormality n (%)	34 (64.15)	/	/
mRS [mean ± SD]	3.21 ± 1.22	/	/
Disease duration (weeks) [median (IQR)]	8 (4-15)	/	/

CSF, cerebrospinal fluid; WBC, white blood cell; MRI, Magnetic Resonance Imaging; EEG, electroencephalography; mRS, modified Rankin Scale.

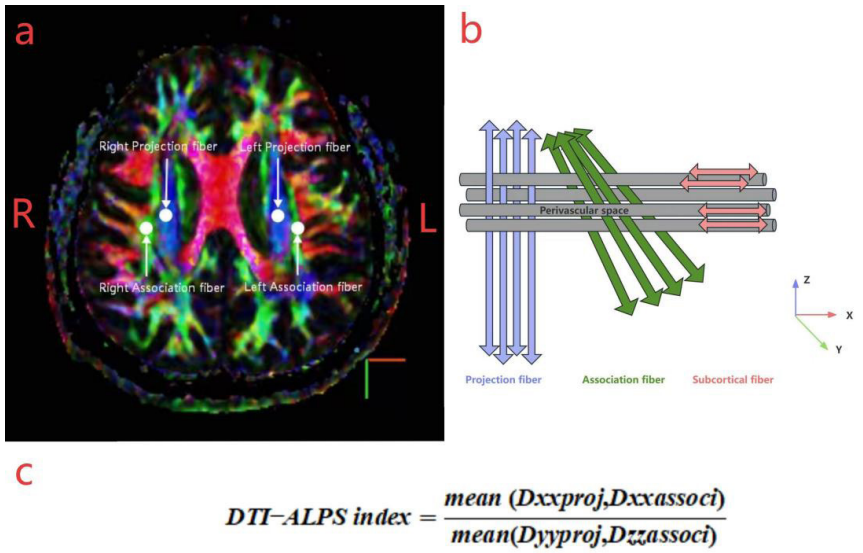

Fig 1. Calculation of ALPS index. Dxxproj and Dxxassoc denote the x-axis diffusivities in the projection and association fibers, respectively, and Dyyproj and Dzzassoc represent the y- and z-axis diffusivities in the corresponding fiber regions.

were analyzed via self-developed pipeline using FMRIB software Library (FSL, Oxford Centre for Functional MRI of the Brain, Oxford, UK) and ITK-SNAP (version 3.8, UPenn amp; UNC, USA). The preliminary processing step involved eddy-current correction, motion correction and brain tissue extraction (BET). After preprocessing, color-coded fractional anisotropy (FA) maps and directional diffusivity maps (along x, y, and z axes) were created during post-processing (Figure 1b). To compute the ALPS index, two circular ROIs (radius = 4 mm) were defined in the projection and association fiber areas bordering the lateral ventricle PVS, where these spaces are well-visualized. To ensure consistency between different observers, two neuroradiologists with 10 and 8 years of professional experience independently identified and outlined the ROIs. To calculate the ALPS index, researchers used a specific mathematical formulation. This index was determined by taking the value of x-axis diffusivities, which is aligned with PVS, and dividing it by the combined mean of y- and z-axis diffusivity values, which are perpendicular to the PVS. As illustrated in Figure 1c, the formula applied is (Dxxproj + Dxxassoc) / (Dyyproj + Dzzassoc). Here, Dyyproj and Dzzassoc represent the x-axis diffusivities in projection and assciation fiber regions respectively, while Dyyproj and Dzzassoc correspond to the y-axis and z-axis diffusivities in the same respective areas.11

Statistical analysis

All analyses were performed in SPSS 26.0 (IBM Corp.), with a significance level of $p < 0.05$. Continuous variables were first tested for normality using the Shapiro-Wilk test. For data that met the normal distribution assumption, they are presented using the mean value along with the standard deviation (SD), and the independent samples t-test was applied to compare differences between groups. Non-normally distributed variables are expressed as median with interquartile range (IQR), and the Mann-Whitney U test was employed for between-group comparisons. For longitudinal assessment of treatment effects, paired t-tests were used to analyze changes from baseline to 4-week follow-up within the same patients. To evaluate the consistency of measurements for the ALPS index across different raters, intraclass correlation coefficients (ICC) were employed. Furthermore, correlation analyses were carried out to explore the association between the ALPS index and various clinical parameters. To address the nature of the data, the correlation analysis employed different statistical methods. Pearson's correlation was selected for variables that met

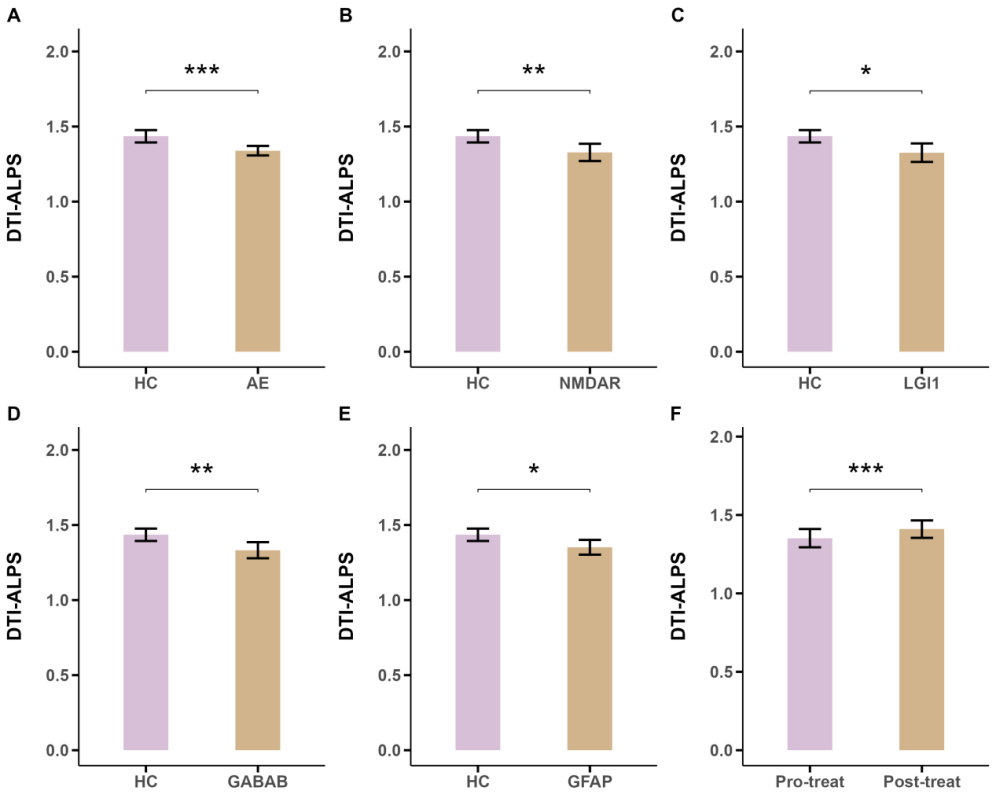

Fig 2. Comparison of ALPS index across AE subtypes and HCs. (A) Comparisons of ALPS index between all AE patients and HCs, $p < 0.001$. (B) Comparisons of ALPS index between NMDAR patients and HCs, $p = 0.0038$. (C) Comparisons of ALPS index between LGI1 patients and HCs, $p = 0.0217$. (D) Comparisons of ALPS index between GABAB patients and HCs, $p = 0.0214$. (E) Comparisons of ALPS index between GFAP patients and HCs, $p = 0.0226$. (E) Comparisons of ALPS index between pro-treatment and Post-treatment, $p < 0.001$.

normal distribution criteria, whereas non-normally distributed variables were analyzed using Spearman's rank correlation.

RESULTS

Study cohort characteristic

The research sample was composed of 53 individuals diagnosed with antibody-positive AE, where 31 were male (accounting for 58.5%) and 22 were female (41.5%). Their average age stood at 35.3 ± 14.7 years. In contrast, the healthy controls (HCs) group included 33 participants (13 males, 39.4%; 20 females, 60.6%) with a mean age of 38.8 ± 11.5 years. The two groups showed no significant differences in age ($p = 0.245$) or sex distribution ($p = 1.000$). For the patient group, the median duration of illness stood at 8 weeks (interquartile range: 4–15), while their mRS assessment at the time of admission was measured as 3.21 ± 1.22. Table 1 presents a summary of the participants, demographic details and clinical characteristics. Following this, every participant went through the entire MRI scanning process without interruption.

The ALPS index showed differences between the AE group and HCs

AE patients demonstrated a significantly lower mean ALPS index compared to HCs (1.34 ± 0.12 vs. 1.43 ± 0.12; independent samples t-test, $p < 0.001$). A visual representation of how the ALPS indices are distributed across two groups is provided in Figure 2A.

Correlation analysis-ALPS index and clinical parameters

Correlation with Disease Severity: A statistically significant negative correlation was observed between ALPS index values and the mRS scores (Pearson's $r = -0.66$, $p < 0.001$), demonstrating

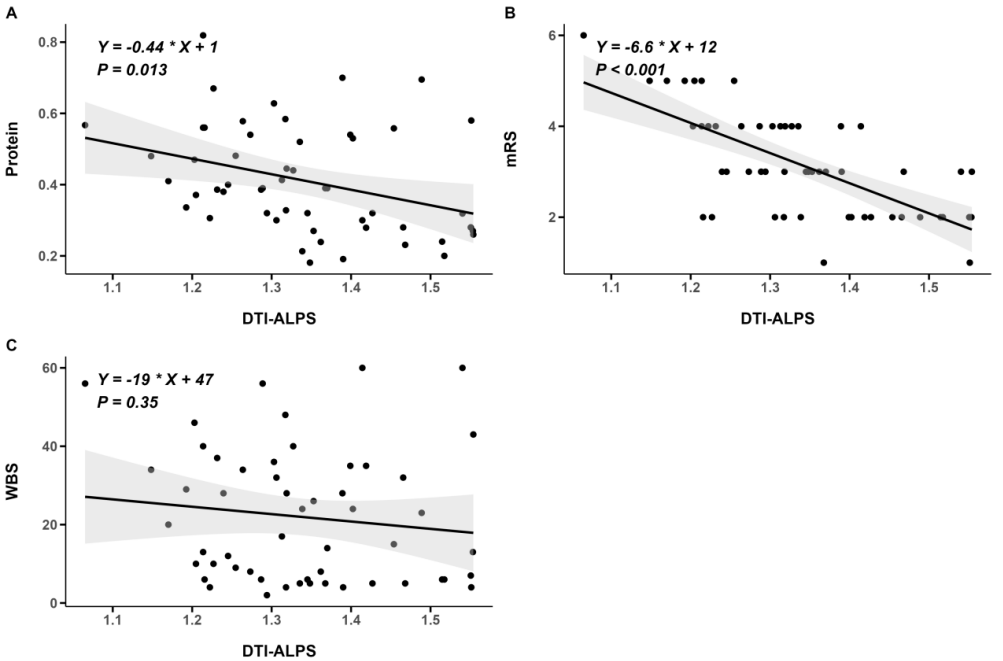

Fig 3. Correlations between ALPS Index and clinical parameters. (A) Scatter plot showing ALPS index vs. CSF protein level (negative correlation). (B) Scatter plot showing ALPS index vs. mRS scores (negative correlation). (C) Scatter plot showing ALPS index vs. WBC count (no significant correlation).

that greater clinical disability is associated with impaired glymphatic system function (Figure 3B).

Correlation with CSF parameters: Analysis of CSF biomarkers revealed a weak but significant inverse relationship between ALPS index and CSF total protein levels (Pearson's r = -0.44, p = 0.013). Conversely, no meaningful association was found between the ALPS index and count of WBC in the CSF (Spearman's r = -0.19, p = 0.35) (Figure 3A, 3C).

Analysis of ALPS index across different AE subtypes and HCs

Anti-NMDAR patients had the lowest ALPS indices (1.31 ± 0.13), significantly lower than HCs (p = 0.0038).

Anti-LGI1 patients also exhibited reduced ALPS indices (1.34 ± 0.09) compared to HCs (p = 0.0217).

Anti-GABABR patients exhibited ALPS indices (1.33 ± 0.08) significantly lower than HCs (p = 0.0214).

Anti-GFAP patients showed intermediate ALPS indices (1.35 ± 0.10), which were still lower than HCs (p = 0.0226) (Table 2, Figure 2B-2E).

ALPS Index and treatment response

Among 20 patients with acute exacerbation (AE), 4 weeks following the start of immunotherapy, they underwent follow-up MRI examinations. Treatment responders (n=20, defined by mRS improvement ≥2 points) demonstrated a significant increase in ALPS index from 1.35 ± 0.13 to 1.41 ± 0.13 (paired t-test, p < 0.001) (Figure 2F).

Reproducibility of ALPS index measurements

Inter-rater reliability for ALPS index quantification was excellent between the two neuroradiologists, as indicated by an intraclass correlation coefficient (ICC) of 0.93 (95% CI: 0.86-0.97; p < 0.001).

DISCUSSION

This research introduces the initial thorough assessment of glymphatic system functionality in patients with AE by means of the non-invasive DTI-ALPS technique. Key observations from the analysis indicate that glymphatic activity is significantly compromised in individuals with AE when compared to HCs, as evidenced by a notable decrease in ALPS indices.[16] Furthermore,

Table 2: ALPS Index comparisons across AE subtypes and HCs

Group	n	ALPS Index (mean ± SD)	P (vs. HC)
HC	33	1.43 ± 0.12	-
All AE Patients	53	1.34 ± 0.12	$p < 0.001$
Anti-NMDAR	20	1.31 ± 0.13	$p = 0.0038$
Anti-LGI1	8	1.34 ± 0.09	$p = 0.0217$
Anti-GABABR	9	1.33 ± 0.08	$p = 0.0214$
Anti-GFAP	16	1.35 ± 0.10	$p = 0.0226$

the degree of glymphatic impairment shows a correlation with progression of clinical symptoms and exhibits variations across different antibody types, with anti-NMDAR encephalitis cases demonstrating the most severe reduction in function. Notably, patients responding to early immunotherapy demonstrate potential recovery of glymphatic function.

The significantly lower ALPS indices in AE patients (1.34 ± 0.12 vs 1.43 ± 0.12 in HCs, $p < 0.001$) strongly suggest compromised glymphatic function in this population. This finding aligns with the growing recognition that neuroinflammatory conditions disrupt the brain's waste clearance mechanisms.[6] The significant negative correlation between ALPS indices and mRS scores ($r = -0.66$, $p < 0.001$) supports the potential involvement of glymphatic dysfunction in the clinical manifestations of AE. This association implies that reduced removal of autoantibodies, inflammatory substances, and metabolic byproducts might worsen neuronal damage and impede healing.[17] The link with CSF protein levels concentrations rather than WBC count further indicates that the biochemical makeup of CSF, rather than solely cellular inflammation, could be a key element in glymphatic dysfunction.[18,19]

Although previous research has not specifically looked into glymphatic function in AE through DTI-ALPS, our results align with studies showing glymphatic system impairment in other neurological disorders.[20-23] The decrease in ALPS index observed in AE patients is more significant than what has been documented in mild cognitive impairment cases but less marked compared to advanced neurodegenerative conditions.[3] This middle range of impairment could suggest that autoimmune-related neuronal dysfunction might be reversible, unlike the progressive nature of neurodegenerative diseases.[24]

The notable severity of glymphatic system dysfunction observed in anti-NMDAR encephalitis warrants heightened consideration. Such a result is consistent with clinical observations that this autoimmune encephalitis subtype typically follows a severe and prolonged progression.[4,25,26] The underlying process could involve the antibodies against NMDAR exerting direct impacts on neuronal function and synaptic plasticity, potentially impairing the neurovascular coupling -a critical driver of glymphatic transport.[5]

Various potential factors could account for glymphatic system impairment noticed in AE

The interplay between neuroinflammation and the malfunction of AQP4 water channels: Pro-inflammatory cytokines and disease-triggering autoantibodies are likely to disrupt the balanced arrangement of AQP4 on astrocytic endfeet, which is a vital factor for the proper operation of glymphatic fluid transport system.[27] Such a disruption might result from either direct antibody interactions or be a consequence of widespread neuroinflammation.[28] Altered sleep-wake patterns: Sleep disruptions are frequently seen in patients with AE, and since the glymphatic system primarily functions during slow-wave sleep stages, these disturbances could have a substantial negative effect on its function.[29] Consequently, the sleep fragmentation often present in AE may lead to a reduction in the clearance of waste products.[30] Modifications in PVS: Long-term inflammation could cause structural changes in PVS, possibly through the process of gliosis or the rebuilding of the

extracellular matrix, thereby forming a physical obstacle to the exchange between CSF-ISF.[31]

Considering the practical applications and upcoming research paths

Our subgroup analysis revealed a link between the improvement of ALPS index and a favorable response to immunotherapy, suggesting that glymphatic function might serve as a flexible indicator for evaluating outcomes.[32] Although this observation is still in its early stages, it opens the idea that boosting glymphatic function could offer a new approach to treating AE.[33] For future research, several important areas need focus: (1) continuously observing glymphatic function through different stages of disease development and recovery[34]; (2) creating specific methods to increase glymphatic clearance in patients with AE[33]; (3) studying how glymphatic activity relates to different cognitive abilities[35]; and (4) applying combined imaging techniques that combine DTI-ALPS with other neuroinflammatory markers.[36,37]

To sum up, this research establishes glymphatic dysfunction as a critical measurable pathological marker in AE. Employing the non-invasive DTI-ALPS technique, we clearly show notable impairment of glymphatic function among AE patients, where degree of impairment closely aligns with progression of clinical symptoms. Notably, patients with anti-NMDAR encephalitis displayed the most severe glymphatic compromise, whereas early immunotherapy responders exhibited promising signs of functional recovery.

When evaluating the outcomes of our research, it is essential to take into account several factors that might restrict the full understanding of the finding. One notable restriction is that, despite being sufficient for initial statistical assessments, the number of participants in the sample hindered more detailed subgroup evaluations. To address these limitations, further research with larger participant groups should be conducted to verify and expand upon our findings. Second, even though patients without apparent structural anomalies were excluded in our research, there exist undetectable microstructural variations by traditional MRI methods that could impact DTI assessment.[38] Third, the inclusion of participants spanning various disease stages, including both initial and log-term phases, might cause inconsistencies in the measurement of ALPS index. Fourth, patients often present with headaches and altered consciousness, which can result in heightened head movement, thereby potentially impairing DTI quantification. Additionally, despite the fact that the DTI-ALPS technique has been confirmed to be effective, it is important to emphasize that this method only offers a non-direct evaluation of glymphatic function and might be prone to confounding factors that have no relation to perivascular flow.[33]

In conclusion, this research presents robust findings revealing notable impairment of the glymphatic system in patients with AE, as measured by the DTI-ALPS index. The observed correlations between glymphatic dysfunction and clinical severity, along with the distinctive patterns across antibody subtypes, suggest that impaired waste clearance could serve as a crucial pathophysiological mechanism in AE. These results confirm that the DTI-ALPS index serves as a significant non-invasive indicator for assessing disease severity and tracking therapeutic outcomes in AE. Subsequent research efforts are required to uncover the exact processes contributing to glymphatic system dysfunction and assess its feasibility as a novel therapeutic approach in the treatment of AE.

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DISCLOSURE

Ethics: Ethics Approval No. II2024-266-01 obtained from the Third Affiliated Hospital of Sun Yat-sen University. All participants provided written informed consent for both study participation and the use of their data in this publication.

Data availability: The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request. Researchers interested in accessing the de-identified data may contact Prof. Lingrong Peng (Email: penglingrong@163.com). All data requests will be reviewed by the research committee to ensure compliance with ethical

standards and data protection regulations

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Conflicts of interest: None

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