Editorial

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Deep cervical lymphaticovenous anastomosis in Alzheimer's disease: A promising frontier or premature enthusiasm?

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SUMMARY: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by β-amyloid accumulation, tau pathology, and impaired metabolic waste clearance. Recent evidence suggests that meningeal lymphatic vessels (MLVs) contribute significantly to the drainage of cerebrospinal and interstitial fluid. Deep cervical lymphaticovenous anastomosis (LVA), a microsurgical technique designed to enhance this drainage, has been proposed as a potential therapeutic strategy for AD. Preliminary findings from exploratory studies in China indicate possible cognitive and biomarker improvements, but current evidence is limited by small sample sizes, non-randomized designs, and methodological variability. Without standardized protocols and rigorous clinical validation, the broader applicability of LVA remains uncertain. Further investigation through multicenter, controlled trials is essential to objectively assessing its safety, efficacy, and clinical relevance in the management of AD.

Keywords: meningeal lymphatic vessels, VEGF-C, Piezo1, metabolic clearance, neurodegenerative disease, surgical intervention

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for 60-70% of all cases worldwide (*1*). As a progressive neurodegenerative condition, it clinically manifests as cognitive decline, behavioral disturbances, and impaired activities of daily living (*2*). Pathologically, it is characterized by extracellular deposition of β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles consisting of hyperphosphorylated tau protein, synaptic dysfunction, and neuroinflammation (*3*). According to the World Alzheimer Report 2023, over 55 million people globally are living with dementia, and this number is projected to exceed 139 million by 2050 (*1*). In China, the prevalence of AD is increasing rapidly due to aging of the population and it affects more than 10 million individuals, making it one of the most burdensome chronic neurological diseases in the country (*4*).

Despite continuous progress in drug development, current treatments for AD remain largely symptomatic, aiming to temporarily improve cognition or delay decline. Cholinesterase inhibitors and NMDA receptor antagonists are commonly used, but they have limited impact on disease progression (*5*). Recently, the exploration of disease-modifying therapies has shifted attention to pathological mechanisms such as impaired clearance of brain-derived metabolic waste, and particularly Aβ and tau aggregates.

Stem cell-based therapies have shown promise in preclinical studies by modulating inflammation, enhancing neuroprotection, and promoting neurogenesis (*6*). In China, policy support for stem cell and exosome-based treatment of neurological diseases is growing. Notably, on March 22, 2025, during the Boao Lecheng Stem Cell Conference, Chinese regulatory authorities announced for the first time the official pathways for approval, pricing, admission criteria, and clinical translation of stem cells projects. Several innovative therapies were granted pilot application status. However, stem cell-based interventions for AD remain in the clinical trial stage and have yet to enter routine clinical practice (*2*).

In this context, a novel microsurgical approach known as deep cervical lymphaticovenous anastomosis (LVA) has garnered increasing attention in China. This technique aims to enhance the clearance of cerebrospinal fluid (CSF) and interstitial fluid (ISF) by reconstructing a drainage route between the meningeal lymphatics and venous system (*7*). Several clinical centers, including those in Hangzhou, Shanghai, Nanjing, Harbin, Zhengzhou, and Zunyi, have launched exploratory studies using LVA in patients with AD (Table 1) (*8-13*). Preliminary results suggest potential improvements in

Table 1. Summary of LVA performed at major clinical centers in China

Facility (*ref.*)	Number of cases (*n*)	Main inclusion criteria	Surgical approach	Postoperative follow-up and preliminary outcomes
Qiushi Hospital, Hangzhou (*8*)	200	Age 40–90; diagnosis >12 months; expected survival >6 months; severe cognitive impairment; imaging evidence of ventricular enlargement or cerebral atrophy; informed consent obtained	Deep cervical lymphaticovenous anastomosis in the level II/III neck region	Cognitive and self-care functions largely restored within 9 months postoperatively
The First People's Hospital of Zunyi (*9*)	100	Age 60-90; IWG-2021 AD diagnostic criteria; experimental (LVA + medication) *vs.* control (medication only); multidimensional cognitive, biomarker, and imaging assessment	Deep cervical lymph node/vessel–venous anastomosis	Experimental group displayed superior improvement on neuropsychological scales, biomarkers, and imaging over 24-month follow-up
Shanghai Ninth People's Hospital (*10*)	10	Age 50–75; MMSE > 10; AD confirmed by PET-MR and CSF testing; no major organ disease; informed consent obtained	Deep cervical lymphaticovenous anastomosis	Over 50% of patients exhibited marked alleviation of symptoms; follow-up of up to 5 months
Zhengzhou Central Hospital (*11*)	100	Not specified; all cases clinically diagnosed with AD	Deep cervical lymphaticovenous anastomosis	Most patients displayed significant alleviation of symptoms postoperatively
The Second Hospital Affiliated with Harbin Medical University (*12*)	100	Moderate-stage AD; exclusion of vascular, toxic, or hypoxic dementia; preoperative cognitive assessment, PET, and CSF Aβ/tau analysis	Deep cervical lymphaticovenous anastomosis	Reported efficacy of 80%; cognitive improvements observed in the majority of patients
Nanjing First Hospital (*13*)	26	PET/MRI-confirmed abnormal deposition of Aβ and tau proteins	Deep cervical lymphaticovenous anastomosis	Preliminary outcomes favorable; marked cognitive improvement tended to be observed

Abbreviations: AD: Alzheimer's disease; Aβ: β-amyloid; CSF: cerebrospinal fluid; IJV: internal jugular vein; IWG: International Working Group; LVA: lymphaticovenous anastomosis; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; PET: positron emission tomography; p-Tau: hyperphosphorylated tau protein.

cognition, imaging biomarkers, and metabolic clearance efficiency (*14*). While preliminary clinical findings from China are intriguing, the field now stands at a critical juncture: will LVA mark a paradigm shift in AD treatment, or have we gotten ahead of the evidence?

2. Anatomical basis and therapeutic mechanism of LVA

The clearance of intracranial metabolic waste has long been a central issue in understanding the pathogenesis of AD (*15*). Traditionally, the central nervous system was believed to lack a conventional lymphatic system, with metabolic waste being primarily eliminated through arachnoid granulations into the venous circulation (*16*). However, recent studies have noted the presence of specialized lymphatic structures in the meninges, known as meningeal lymphatic vessels (MLVs), which connect with the deep cervical lymph nodes (dcLNs) (*17,18*). This discovery provides anatomical evidence supporting the drainage of CSF and ISF from the brain (Figure 1).

Imaging data suggest that CSF efflux *via* perisinusal and paravascular meningeal lymphatic pathways may be significantly greater – potentially up to 180% – than drainage through basal dural lymphatic routes (*19*). Approximately 50% of CSF clearance is believed to occur through cervical lymphatic drainage into the cervical lymph nodes (*18,20,21*). The remaining CSF is routed through the spinal cord to mediastinal, iliac, and sacral lymph nodes (*22,23*), or drains *via* perivascular spaces (*21*). Toxic molecules including Aβ, hyperphosphorylated tau, inflammatory mediators, and other metabolic byproducts are transported out of the brain through these lymphatic channels (*17,24-26*). When the meningeal lymphatic system is impaired or obstructed, clearance efficiency declines, resulting in the accumulation of neurotoxic waste in the brain, activation of neuroinflammation, and the progression of neurodegeneration (*27*). These processes may play a key role in the pathogenesis and exacerbation of AD (*26,28*).

LVA has been proposed as a surgical intervention grounded in the clearance pathway hypothesis mentioned earlier. Using microsurgical techniques, LVA establishes an anastomosis between downstream lymphatic structures – such as deep cervical lymphatic vessels or nodes – and adjacent venous branches (*e.g.*, the internal jugular vein, IJV) to create a low-resistance drainage route, thereby enhancing the efflux of brain-derived metabolic waste (*7,29*). Intraoperatively, sodium fluorescein or indocyanine green (ICG) is often used in lymphatic mapping to assist in identifying functional lymphatic vessels (*30*). Under a high-magnification microsurgical field, lymphaticovenous anastomoses are typically performed using vessels with diameters between 0.5-0.8 mm (*14*). The most commonly employed techniques include end-to-side and end-to-end anastomoses, both of which are designed to minimize venous reflux and

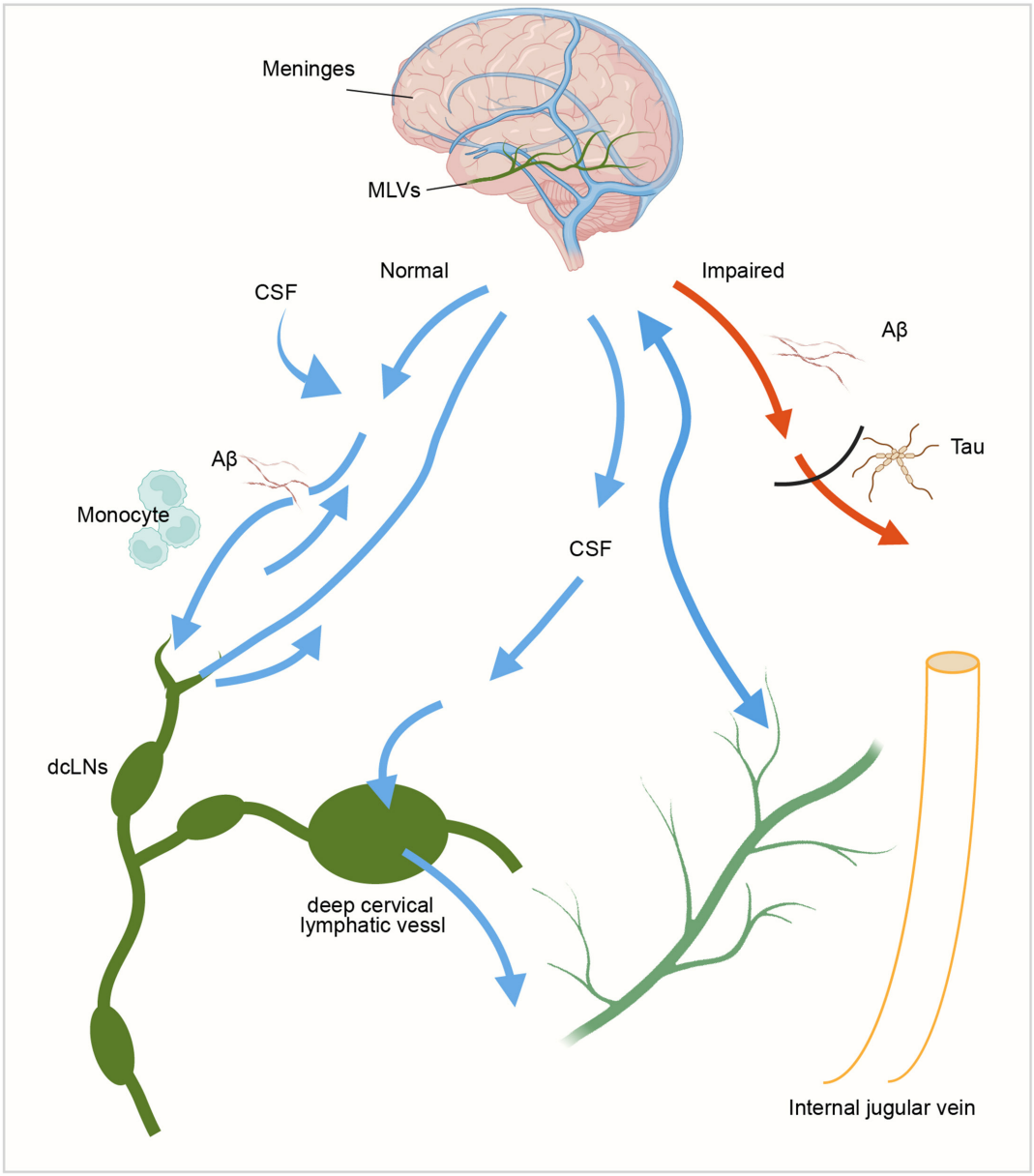

Figure 1. Schematic diagram of the MLVs and pathways of metabolic waste clearance. *Notes*: Green lines indicate lymphatic routes; blue, venous structures; arrows, waste flow direction. Aβ, β-amyloid; CSF, cerebrospinal fluid; dcLNs, deep cervical lymph nodes; MLVs, meningeal lymphatic vessels; p-Tau, hyperphosphorylated tau protein; IJV, internal jugular vein.

maintain the long-term patency of the connection (*7,14*). With the development of supermicrosurgery, some studies have explored finer anastomoses involving vessels smaller than 0.5 mm, which may enhance conduit stability and reduce tissue reactivity.

In patients with AD, functional evaluation of the MLV system can be performed using contrast-enhanced magnetic resonance imaging (MRI) (*31*). Imaging studies have demonstrated that MLV function is significantly impaired in AD, and particularly in its moderate to advanced stages, with lymphatic flow decreasing by nearly 40% compared to age-matched controls (*26,32*). Further evidence suggests that CSF flow disturbances are strongly correlated with cognitive decline and that the efficiency of Aβ clearance is positively associated with MLV functionality (*26*).

In an animal model of AD, reduced MLV function is directly associated with increased Aβ accumulation in the cortex and hippocampus, leading to neuronal damage and cognitive impairment (*33*). The decline in MLV function not only impairs the clearance of Aβ and other metabolic waste but also triggers neuroinflammatory responses. Studies have shown that during the progression of AD, VEGF-C expression in meningeal tissues declines significantly, leading to impaired lymphangiogenesis, reduced Aβ clearance capacity, and localized neurotoxic inflammation (*33*). Treatment with exogenous VEGF-C has been shown to improve Aβ clearance by over 40%, along with a significant enhancement in cognitive performance (*34*).

Additionally, mechanical stress induced by CSF flow dynamics may regulate VEGF-C expression and thereby modulate lymphatic function indirectly (*35*). In 5xFAD mice, ablation of MLVs results in a significant increase in meningeal macrophage populations within just one week, indicating that Aβ accumulation in dysfunctional MLVs induces local inflammation (*26*). Subsequent studies have demonstrated that restoring MLV function can effectively suppress microglial overactivation and attenuate chronic neuroinflammation within the brain (*36*). Other findings suggest that CSF hydrodynamic abnormalities associated with AD may impair Piezo1 channel activation, thereby reducing the mechanosensory capacity of MLVs, impairing waste clearance, and promoting Aβ deposition in brain tissues (*37*).

In summary, dysfunction of the MLV system is closely associated with impaired metabolic waste clearance and heightened neuroinflammation in AD. Given this mechanism, LVA represents a novel surgical intervention aimed at reestablishing lymphatic-venous drainage and improving intracranial metabolic homeostasis. It is rapidly gaining attention as a promising exploratory approach in the treatment of AD.

3. Clinical challenges and future directions

Currently, the use of LVA to treat AD remains in an exploratory phase. Most clinical studies conducted to date are observational or non-randomized, with small sample sizes, heterogeneity in study design, and inconsistent outcome measures. Critically, there is a lack of high-quality, multicenter, double-blind, prospective randomized controlled trials (RCTs), which significantly limits the robustness and generalizability of the evidence base. Given that AD is a slowly progressive neurodegenerative condition, short-term follow-up is insufficient to fully evaluate the long-term effects of a surgical intervention on disease trajectory. Large-scale, methodologically rigorous, and long-duration studies need to be promptly conducted to assess the sustainability of therapeutic benefits, clarify patient eligibility criteria, compare the efficacy of different surgical techniques, and document postoperative complications. A structured and scientifically sound research framework is essential.

Notably, there is substantial variability among clinical centers in terms of preoperative assessment and inclusion criteria. The absence of standardized patient selection protocols and clearly defined inclusion and exclusion criteria undermines the reliability of the current findings. Given the substantial clinical and pathological heterogeneity inherent in AD, whether LVA offers universal benefit remains unclear. Future efforts should prioritize the development of individualized screening models incorporating pathology subtypes, neuroimaging profiles, CSF dynamics, biomarker levels, and cognitive assessments. Such precision-based approaches would optimize patient selection, enhance treatment efficacy, and minimize unnecessary or ineffective interventions.

From a technical perspective, LVA is substantiated by a well-defined anatomical rationale, but there are still inconsistencies in its implementation. The type of anastomosis (*e.g.*, end-to-end, end-to-side, lymphatic valve reconstruction), choice of target vessels, intraoperative imaging techniques, and postoperative assessment protocols vary among facilities. Given that the procedure requires high-level supermicrosurgical skills and is technically demanding, differences in the surgeon's experience and technique may directly impact outcomes. To ensure safety, reproducibility, and broader adoption, a unified set of technical guidelines and a formalized training and credentialing system should be established.

Ethical and regulatory considerations are equally critical. As an invasive intervention, and particularly one in a population with cognitive impairment, the ethical performance of LVA must be rigorously upheld. Comprehensive informed consent procedures are essential, ensuring that patients and their caregivers fully understand the purpose, anticipated benefits, uncertainties, and potential risks of the surgery.

Despite these challenges, LVA represents a novel intervention that seeks to restore the brain's metabolic clearance pathways—an emerging paradigm in the management of AD. Future studies should explore the potential synergy between LVA and other therapeutic strategies, including stem cell therapy (*6*), anti-Aβ monoclonal antibodies (*38,39*), and neurorehabilitation techniques such as sensory-paired associative stimulation (SPA) (*40*). International research, including work by Louveau *et al*. (*41*) and Iliff *et al*. (*42*), has laid a theoretical foundation for the role of the MLV system in neurological disease. Future clinical trials of LVA should adopt internationally benchmarked methodologies, including multicenter, double-blind, and stratified randomization designs, to elevate the level of evidence and facilitate a global consensus.

4. Conclusion

LVA has emerged as a promising microsurgical technique based on the MLV system's role in clearing brain metabolic waste. Early clinical studies suggest that LVA may improve waste drainage and delay disease progression in AD, with preliminary evidence supporting its short-term efficacy and safety. China is at the forefront of global exploration in this area, with multiple centers reporting initial procedural experience and technical innovation.

Nevertheless, LVA remains in the early stages of clinical validation. Most existing studies are limited in sample size and methodological rigor and lack standardized protocols or high-quality evidence to support widespread clinical adoption.

In summary, LVA introduces a novel therapeutic

concept centered on reconstructing brain clearance pathways. It expands the scope of AD treatment beyond conventional pharmacology. As a technology still under evaluation, its future clinical relevance will depend on in-depth research into mechanisms, rigorous validation in clinical trials, and collaborative development of standardized procedures. Only through the convergence of verified efficacy, technical standardization, and robust regulatory oversight can LVA attain a clearly defined role in the evolving multimodal treatment landscape of AD.

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