Research and Practice

Cervical Shunting to Unclog Cerebral Lymphatic Systems: A New Possibility for Alzheimer's Treatment

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Key highlights

- The cerebral glymphatic system serves as a pathway for the brain to clear pathological proteins, and its clearance capacity is impaired in patients with Alzheimer's disease.
- We have developed a surgical procedure, Cervical Shunting to Unclog Cerebral Lymphatic Systems (CSULS), designed to enhance the drainage of the cerebral glymphatic system and accelerate the clearance of pathological proteins such as Aβ and tau in the brain.
- Preliminary research findings suggest that the CSULS surgery has improved cognition and reaction in patients, reduced Aβ and tau protein burden, and is a promising method for slowing the progression of Alzheimer's disease.
- More rigorous evidence from randomized controlled trials (RCTs) needs to be developed to affirm the short-term and long-term effectiveness of CSULS.

Dementia has become a formidable global health challenge, with an estimated 55.2 million individuals worldwide affected, according to the 2022 blueprint for dementia research issued by the World Health Organization. The prevalence rates vary across regions, ranging from 2.9% in Southeast Asia to 6.5% in Europe and between 3.1% and 5.7% in other areas. Projections indicate that the number of people afflicted with dementia will escalate to approximately 78 million by the year 2030. Moreover, the economic burden associated with providing medical care, social services, and informal caregiving for individuals with dementia is anticipated to surpass US$ 2.8 trillion globally—a situation that carries profound implications for individuals, families, and society at large. Alzheimer's disease (AD), the most common form of dementia, mirrors this escalating trend and presents a growing global challenge.

The etiology of AD is multifaceted and not yet fully understood. Beyond the pivotal proteins beta-amyloid (Aβ) and tau, contributing factors include acetylcholine deficiency, neuroinflammation, oxidative stress, glutamate imbalance, insulin resistance, dysbiosis in the gut microbiome, disruption of cholesterol homeostasis, impairment of mitochondrial function, and abnormalities in autophagy. Recent studies highlight that the impairment of brain glymphatic system's clearance capacity may serve as a crucial factor in the deposition of pathological proteins in AD. In contrast to the conventional cerebrospinal fluid (CSF) circulation model, the updated glymphatic

model proposes that CSF can permeate into the brain parenchyma through perivascular spaces and exchange with interstitial fluid, thereby eliminating Aβ, tau protein, and other interstitial solutes towards the cisternal CSF compartments. Research has shown that compromised glymphatic clearance precedes amyloid plaque formation in animal models of AD.

Based on the fact that neck lymph nodes receive CSF from the cerebral glymphatic system, we postulated that lymphatic trunk decompression and lymphatic-venous anastomosis (LVA) could facilitate substance exchange in the cerebral glymphatic system, potentially accelerating clearance of harmful Aβ and tau proteins. In collaboration with a surgeon specializing in oral and maxillofacial tumors and LVA microvascular surgery, we developed the Cervical Shunting to Unclog Cerebral Lymphatic Systems (CSULS) procedure utilizing microvascular surgical techniques to create an LVA connection between bilateral deep cervical lymphatic vessels and veins, thereby decompressing the lymphatic trunk and allowing high-pressure lymphatic fluid to flow into low-pressure venous system. This minimally invasive procedure aims to enhance protein clearance from cerebral glymphatic system to oral/maxillofacial vessels, reducing accumulation of harmful proteins in brain.

As of August 18, 2024, a total of 20 individuals have undergone the CSULS procedure. The primary postoperative complication observed was delirium occurring within the initial 24 hours following surgery, potentially associated with anesthesia administration. However, this delirium resolved within a span of 72 hours. No other adverse reactions were reported. Encouraging preliminary findings indicate that cognitive abilities exhibited slight enhancements in most patients, particularly in attention and reaction speed domains. Furthermore, nursing staff predominantly noted improvements in language skills and mood among the patients.

Currently, we have completed the 3-month follow-up for four patients, encompassing neuropsychological assessments, ^{18}F-FDG PET/MR scans, CSF analyses to detect Aβ42/Aβ40, t-tau, and p-tau181 levels, as well as ^{18}F-AV45 PET and ^{18}F-PI2620 PET imaging to monitor alterations in brain Aβ and tau proteins. The index of diffusion tensor image analysis along the perivascular space (DTI-ALPS) exhibited a significant increase in all four patients, indicating effective enhancement of glymphatic drainage through surgical intervention. The mini-mental status examination (MMSE) score demonstrated an improvement of 2-3 points. Moreover, postoperative activities of daily living (ADL) scores decreased by 2-5 points signifying enhanced daily functioning ability. CSF analysis revealed an elevated Aβ42/Aβ40 ratio alongside reduced t-tau and p-tau181 levels; reductions in standardized uptake value ratios (SUVr) observed on both ^{18}F-AV45 PET and ^{18}F-PI2620 PET imaging provided objective evidence of diminished pathological protein burden such as Aβ and tau proteins within the patient's brain. Furthermore, overall improvements in brain glucose metabolism were evident from the findings obtained via ^{18}F-FDG PET imaging. However, despite the reduction in AV45 uptake observed across almost all brain regions, there was no

significant improvement in some brain regions such as superior parietal cortex, posterior medial temporal cortex, posterior cingulate cortex and primary visual cortex. This suggests that the clearance of pathological proteins may not fully restore brain metabolism in these specific regions in the short term. It remains to be investigated whether any long-term effects will emerge through extended follow-up studies.

CSUL surgery has shown promising initial therapeutic effects in patients with AD, indicating significant potential as a viable treatment option. Moving forward, we plan to conduct long-term follow-up assessments to evaluate the sustained therapeutic benefits and validate these findings in a larger cohort of individuals diagnosed with AD.

Peizhe Yuan, MD, has a medical doctorate from Huazhong University of Science and Technology and has been a postdoctoral researcher in the Nuclear Medicine Department of Shanghai Jiao Tong University School of Medicine affiliated with Renji Hospital since 2023. His main research interest is PET imaging analysis related to neurodegenerative diseases, particularly Alzheimer's disease.