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Clinical Study of 60 Cases of Deep Cervical Lymphatic-Venous Anastomosis for the Treatment of Alzheimer's Disease

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Abstract: *Objective*: To analyze the therapeutic effect of deep cervical lymphatic-venous anastomosis (LVA) on Alzheimer's disease (AD). *Methods*: 120 patients with AD who were admitted to the hospital between December 2022 to December 2024 were selected and randomly divided into two groups using a random number table. The experimental group received LVA treatment, while the control group received transcranial magnetic stimulation combined with medication. The total effective rate, cognitive function score, language expression, cerebrospinal fluid biomarkers, and adverse reaction rate were compared between the two groups. *Results*: The total effective rate of the experimental group was higher than that of the control group. The cognitive function score and cerebrospinal fluid biomarkers of the experimental group after treatment were better than those of the control group ($P < 0.05$). The adverse reaction rate in the experimental group was similar to that in the control group ($P > 0.05$). *Conclusion*: LVA can improve the clinical efficacy of patients with AD, enhance their cognitive function and language expression, regulate the level of cerebrospinal fluid biomarkers, and has high surgical safety.

Keywords: Deep cervical lymphatic-venous anastomosis; Alzheimer's disease; Transcranial magnetic stimulation; Medication

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1. Introduction

Alzheimer's disease (AD) is a highly concealed neurological disease characterized by progressive degeneration. Its symptoms include decreased executive function, memory impairment, and behavioral changes, which can easily lead to diseases such as senile dementia [1–3]. The commonly used treatments for this disease are oral medications such as donepezil and sodium oligomannate, which can nourish nerves and have a strong regulatory effect on

the microbiome-gut-brain axis, thereby reducing disease symptoms [4–5]. Transcranial magnetic stimulation is a physical therapy for this disease that can electromagnetically stimulate brain tissue to enhance neuronal activity and improve patients' cognitive function. However, the above therapies have limitations in terms of radical treatment [6–8]. LVA is a novel microsurgical procedure that involves anastomosing deep cervical lymphatics and jugular veins to promote lymphatic circulation and clear waste, pathogenic factors, and toxins from the brain, such as Aβ protein and Tau protein, thereby controlling the disease [9]. Based on this, 120 patients with AD were selected for this study to evaluate the therapeutic effect of LVA.

2. Materials and methods

2.1. General information

A total of 120 patients with AD admitted to the hospital between December 2022 to December 2024 were selected and randomly divided into two groups using a random number table. The control group consisted of 60 patients, including 33 males and 27 females, with ages ranging from 50 to 78 years old and a mean age of 62.18 ± 3.78 years. The experimental group also consisted of 60 patients, including 34 males and 26 females, with ages ranging from 48 to 77 years old and a mean age of 62.31 ± 3.82 years. There was no significant difference between the two groups ($P > 0.05$).

Inclusion criteria: Age <90 years old; normal liver and kidney function; newly diagnosed patients; meeting the indications for drug therapy, physical therapy, and surgical treatment; complete basic information; and informed consent for the study. Exclusion criteria: The etiology of cognitive impairment is cerebrovascular disease, etc.; Other neurological diseases such as Parkinson's disease; Combined with severe infection; Difficult to tolerate lumbar puncture; Withdrawal in the middle of the study.

2.2. Methods

The control group received transcranial magnetic stimulation combined with drug therapy. A transcranial magnetic stimulator was used, targeting the bilateral prefrontal lobes with a coil diameter of 12 cm and a frequency of 10 Hz. Stimulation was applied for 5 seconds, followed by a 25-second rest, with 30 repetitions per session. Treatment was administered 5 days per week for a total of 12 weeks. Additionally, patients received oral administration of donepezil hydrochloride at a dose of 5 mg once daily, which was increased moderately after 4 weeks of treatment, with a maximum daily dose of 10 mg. They also took sodium oligomannate at a dose of 450 mg twice daily. Both medications were continued for 12 weeks.

The experimental group underwent LVA treatment. Patients were positioned in a supine position, and marks were made along the anterior and posterior borders of the sternocleidomastoid muscle. High-frequency ultrasound was used to scan the deep cervical lymph nodes at the marked sites, evaluate the branching and course characteristics of the external jugular vein, and measure the specific caliber of the external jugular vein. Under general anesthesia, bilateral LVA treatment was performed. An incision of approximately 5cm was made in the middle of the posterior border of the sternocleidomastoid muscle. Indocyanine green (3 ml) was injected into the subcutaneous tissue behind the ear, the root of the mastoid process, and the angle of the jaw for lymphangiography. The platysma muscle was incised along the incision, and dissection was performed deep to expose the superficial cervical plexus nerve and external jugular vein. On the basis of protecting the great auricular nerve, the posterior border of the sternocleidomastoid muscle was identified, and the muscle was separated. The muscle tissue was

lifted forward appropriately, and the carotid sheath was dissected to expose the lymph nodes in zone III outside the lateral region of the internal jugular vein. The specific morphology of the lymph nodes and the characteristics of the lymphatic vessel course were evaluated. The platysma muscle was dissected, and the anterior border of the sternocleidomastoid muscle was identified. After separating the anterior border of the sternocleidomastoid muscle, the muscle was lifted backward to expose the lymph nodes (zone III) in the medial region of the vein. Dissection was performed toward the head to fully expose the lymph nodes in zone II. A fluorescence microscope was used to observe the lymph node development area and make clear markings. The external and internal jugular veins were dissected, and the lymph nodes (zone III) were also dissected while protecting the thick lymphatic vessels. The developed lymph nodes were moderately resected, and a cross-section was made to drain the lymph fluid. If the lymph fluid was clear, it indicated that the lymph node function was normal. The internal jugular vein or adjacent veins were taken, and the veins at both ends were clamped using venous clamps (the internal jugular vein was directly clamped on the lateral wall using a bulldog clamp). The vein was longitudinally incised with a length equivalent to the diameter of the lymphatic vessel. The outer membranes of the vein and lymph node cross-section were sutured with nylon sutures (single strand, 11-0), and end-to-side anastomosis was performed. The venous clamps were removed, and the anastomotic stoma was checked for leakage. Additional indocyanine green (0.1 ml) was injected behind the ear, and the shunt situation of the lymph fluid was evaluated under a fluorescence microscope. Due to the small movable range and large volume of lymph nodes in zone II, puncture was performed using a 16-gauge needle. The branch of the internal jugular vein and the outer membrane of the hole were sutured with nylon sutures (11-0), and end-to-end anastomosis treatment was performed. The wound was irrigated, and the bleeding was stopped. A drainage tube was placed, and the incision and platysma tissue were sutured in layers with tension reduction. Low molecular weight heparin was continuously administered for anticoagulation for 48 hours, and the patient's signs were monitored. The drainage tube could be removed 48 hours after surgery.

2.3. Observation indicators

2.3.1. Cognitive function scores

Mini-mental state examination (MMSE): Including orientation, recall, and language ability, with a total score of 30, and cognitive function is positively scored; Montreal cognitive assessment (MoCA): Including memory, executive function, and visual-spatial skills, with a total score of 30, and cognitive function is positively scored; Neuropsychiatric inventory (NPI): Including 12 items such as delusions, hallucinations, and anxiety, with a total score of 144 (each item scores 12), and cognitive function is negatively scored.

2.3.2. Cerebrospinal fluid biomarkers

Lumbar puncture was performed on an empty stomach, and 6 ml of cerebrospinal fluid was taken. The fluid was centrifuged for 15 minutes at 2000 r/min and placed at 4°C for 1 hour. The supernatant was taken, and the levels of beta-amyloid protein 1-40 (Aβ1-40), Aβ1-42, phosphorylated tau protein (P-tau), and total tau protein (T-tau) were evaluated by enzyme-linked immunosorbent assay.

2.3.3. Adverse reaction rate

The incidence of nausea, vomiting, dizziness, infection, diarrhea, hematoma, and poor wound healing was observed.

2.4. Therapeutic effect evaluation criteria

Significant effect means significant improvement in symptoms/signs, normal social skills, and ability to live independently; Effective means improvement in symptoms/signs, recovery of social skills, but poor self-care ability; Ineffective means no improvement in symptoms/signs, social skills, or self-care ability.

2.5. Statistical analysis

The data was processed by SPSS 28.0 software. Measurement values were compared/tested by t-value, and count values were compared/tested by chi-square value. Statistical significance was considered when the *P*-value was less than 0.05.

3. Results

3.1. Comparison of the total effective rate between the two groups

The total effective rate of the experimental group was higher than that of the control group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of total effective rate between the two groups [n/%]

Group	Number of cases	Markedly effective	Effective	Ineffective	Total effective rate
Experimental group	60	35 (58.33)	24 (40.00)	1 (1.67)	98.33 (59/60)
Control group	60	33 (55.00)	20 (33.33)	7 (11.67)	88.33 (53/60)
x^2					4.821
P					0.028

3.2. Comparison of cognitive function scores between the two groups

Before treatment, there was no difference in cognitive function scores between the two groups ($P > 0.05$). After treatment, the cognitive function score of the experimental group was better than that of the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of cognitive function scores between the two groups [Mean ± SD, points]

Group	Number of cases	MMSE score		MoCA score		NPI score	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	60	20.15 ± 2.65	26.95 ± 3.12	11.53 ± 2.15	25.04 ± 2.91	92.53 ± 7.15	52.98 ± 5.07
Control group	60	20.11 ± 2.62	24.02 ± 3.10	11.51 ± 2.13	23.01 ± 2.88	92.48 ± 7.11	57.13 ± 5.18
t		0.083	5.160	0.051	3.841	0.038	4.435
P		0.934	0.000	0.959	0.000	0.969	0.000

3.3. Comparison of cerebrospinal fluid biomarkers between the two groups

Before treatment, there was no difference in cerebrospinal fluid biomarkers between the two groups ($P > 0.05$). After treatment, the cerebrospinal fluid biomarkers of the experimental group were better than those of the control group ($P < 0.05$), as shown in **Table 3**.

Table 3. Comparison of cerebrospinal fluid biomarkers between the two groups [Mean ± SD]

Group	Number of cases	Aβ1-40 (ng/ml)		Aβ1-42 (ng/ml)		P-tau (pg/ml)		T-tau (ng/ml)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	60	7.98 ± 1.25	7.35 ± 0.41	0.26 ± 0.08	0.35 ± 0.10	77.53 ± 6.48	50.48 ± 4.26	0.55 ± 0.10	0.23 ± 0.08
Control group	60	7.96 ± 1.27	7.72 ± 0.45	0.25 ± 0.09	0.30 ± 0.07	77.51 ± 6.42	55.13 ± 4.31	0.54 ± 0.11	0.37 ± 0.06
t		0.087	4.708	0.643	3.173	0.017	5.944	0.521	10.844
P		0.931	0.000	0.521	0.002	0.986	0.000	0.603	0.000

3.4. Comparison of adverse reaction rates between the two groups

The adverse reaction rate in the experimental group was similar to that in the control group ($P > 0.05$), as shown in **Table 4**.

Table 4. Comparison of adverse reaction rates between the two groups [n/%]

Group	Number of cases	Nausea and vomiting	Dizziness	Infection	Diarrhea	Hematoma	Poor wound healing	Incidence rate
Experimental group	60	0	0	1 (1.67)	0	1 (1.67)	1 (1.67)	5.00 (3/60)
Control group	60	1 (1.67)	1 (1.67)	1 (1.67)	1 (1.67)	0	0	6.67 (4/60)
x^2								0.152
P								0.697

4. Discussion

Alzheimer's disease (AD) is a cognitive impairment disease with a high incidence rate. Its early stage is asymptomatic, making diagnosis challenging [10–11]. The pathogenesis of AD is complex, involving genetic factors and neurotransmitter disorders, and conventional treatment often involves oral medication [12–13]. Donepezil, a commonly used cholinesterase inhibitor, effectively inhibits acetylcholinesterase in brain tissue, promoting acetylcholine hydrolysis and improving cognitive and motor functions [14]. Sodium oligomannate, a novel drug for AD, targets the brain-gut axis, corrects intestinal flora imbalance, and enhances cognitive function [15–16]. Combined with transcranial magnetic stimulation, it can stimulate the cerebral cortex, improve brain metabolism, enhance interaction between subcortical nuclei and the cerebral cortex, restore the original structure of nerve cells, and alleviate disease symptoms [17]. These therapies, based on traditional pathogenic mechanisms of AD, can stabilize the condition but often have limited long-term efficacy [18–20].

In recent years, clinical medicine has deeply explored the pathological basis of AD, identifying abnormal meningeal lymphatic function as a risk factor [21]. Improving meningeal lymphatic function could potentially slow disease progression [22]. Additionally, lymphatic plexus degeneration is another etiological factor. The nasopharyngeal region, rich in lymphatic plexuses, facilitates cerebrospinal fluid (CSF) outflow. Degeneration of these plexuses can impede CSF outflow. Based on these theories, this study implemented lymphovenous anastomosis (LVA) for AD patients [23–25]. LVA involves anastomosing deep cervical lymph nodes to the internal jugular vein, enabling lymph fluid to flow back into the vein. This utilizes the pressure difference between lymph

fluid and venous blood to clear amyloid-beta protein and tau protein from the lymph fluid. LVA safely and effectively drains lymph fluid through deep cervical lymphatics, removing toxic proteins.

Results showed that the experimental group had a higher total effective rate than the control group. After treatment, the experimental group had higher MMSE and MoCA scores and a lower NPI score. Additionally, the experimental group had lower levels of Aβ1-40, P-tau, and T-tau, and higher levels of Aβ1-42 ($P < 0.05$). The adverse reaction rate in the experimental group was similar to the control group ($P > 0.05$). During LVA surgery, high-frequency ultrasound is used to observe the lymphatic system's functional status, revealing its location, structure, and size. This helps assess the internal jugular vein's course and variability, enabling surgical plan design [26]. Lymphangiography involves injecting indocyanine green into the lymphatic system, facilitating visualized anastomosis and assessing CSF patency post-surgery, ensuring clinical efficacy [27–29]. LVA's brain drainage mechanism lowers intracranial lymphatic pressure, effectively anastomosing cervical lymph nodes and regional veins, thereby alleviating symptoms and improving cognitive function. Furthermore, guided by high-frequency ultrasound and lymphangiography, LVA boasts high precision and minimal intraoperative damage, reducing postoperative complications like hematoma [30]. Studies have shown that meningeal lymphatic function correlates with age, with older individuals experiencing more significant decline, strongly linked to AD. Currently, LVA therapy is being clinically explored to reduce cognitive impairment and alleviate AD symptoms [31]. According to cell research, LVA involves a clear mechanistic loop: meningeal lymphatics → interleukin-6 → synapses → cognition. Future research could integrate LVA surgery with brain lymphatic imaging and cognitive assessment, aiming to rebuild the brain microenvironment, delay cognitive decline, and achieve optimal therapeutic outcomes.

5. Conclusion

In summary, LVA is highly effective in treating AD patients, improving cognitive function, restoring CSF patency, and not increasing postoperative adverse reactions, highlighting its surgical advantages.

Disclosure statement

The authors declare no conflict of interest.

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