MEDS Chinese Medicine (2025)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2025.070306
ISSN 2616-1753 Vol. 7 Num. 3

Study on TCM Stepwise Intervention Strategy for Amyotrophic Lateral Sclerosis Based on the Progressive Theory of "Zongqi - Weiqi - Yuanqi": Integration of Clinical Evidence and Mechanism Discussion

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Keywords: Amyotrophic Lateral Sclerosis; Zongqi; Weiqi; Yuanqi; Lung - Spleen Theory; Spleen - Kidney Theory; Stepwise Intervention; Traditional Chinese Medicine

Abstract: This study investigates a Traditional Chinese Medicine (TCM) stepwise intervention strategy for amyotrophic lateral sclerosis (ALS) based on the progressive theory of "Zongqi–Weiqi–Yuanqi." Literature from the past 15 years was systematically reviewed to reconstruct disease evolution and evaluate therapeutic efficacy. In the early stage, Zongqi collapse is characterized by abnormal respiratory muscle function (87.9%), which precedes measurable pulmonary impairment (52.3%). In the middle stage, Weiqi dysfunction arises. The spleen–lung invigorating method reduces ALSFRS-R monthly decline to 0.64–0.66 points by inhibiting p38 MAPK phosphorylation and suppressing inflammatory cascades. In advanced stages, Yuanqi decline dominates, and spleen–kidney tonification protects neurons via activation of PINK1/Parkin-mediated mitophagy. Internal–external combined therapy further improves outcomes, increasing the total effective rate to 88.46%. Based on these findings, a stepwise framework—"cultivating Zongqi, consolidating Weiqi, and preserving Yuanqi"—is proposed to align therapeutic strategies with disease progression. This model provides a systematic explanation of ALS pathogenesis and offers a structured clinical pathway for precision TCM treatment.

1. Zongqi Sinking: TCM Essence and Clinical Verification of Respiratory Impairment in ALS

The pathological essence of early respiratory dysfunction in ALS can be deeply interpreted through the theory of "Zongqi dysfunction". In TCM theory, Zongqi is formed by the combination of clear qi from nature inhaled by the lung and food essence qi transformed by the spleen and stomach. It accumulates in the chest, travels upward to the respiratory tract to regulate breathing, and penetrates into the heart vessels to promote qi and blood circulation, serving as a key factor in maintaining respiration and systemic qi movement. Studies by Hong Yiming et al. and Zhou Mingjuan et al. have jointly revealed that abnormal respiratory muscle function (87.9%) occurs significantly earlier than pulmonary function impairment (52.3%), and the decline of MIP and MEP

is more severe in patients with bulbar onset (P<0.05). This is highly consistent with the functional positioning of "Zongqi traveling through the respiratory tract to regulate breathing" — Zongqi sinking directly leads to the decline of the respiratory-swallowing axis function, manifested as dysarthria, dysphagia, and respiratory muscle weakness [2-3]. The misdiagnosis cases reported by Liu Changmao further confirm that early respiratory symptoms are easily misdiagnosed as pulmonary infection, precisely because Zongqi dysfunction is characterized by "hidden symptoms and deep disease location [4] ". These clinical phenomena are not isolated but collectively indicate the core position of Zongqi deficiency as the initiating pathogenesis of ALS.

2. Lung-Spleen Co-treatment: A Logical Closed Loop from Clinical Efficacy to Anti-inflammatory Mechanisms

In TCM theory, the lung governs qi and controls respiration, while the spleen is responsible for transporting and transforming water and grain essence. The two are closely related, as encapsulated in the principle that "the spleen is the source of qi production, and the lung is the pivot of qi management." The water and grain essence transformed by the spleen serves as the material basis for the lung's function of governing qi, and the normal dispersion and descent functions of the lung also facilitate the spleen's transportation and transformation. The approach of "treating the lung and spleen concurrently" is based on this theory, emphasizing the regulation of the spleen's transportation to nourish lung qi, while promoting the dispersion and descent of lung qi to aid the spleen's transportation, thereby achieving a synergistic balance between lung and spleen functions. The rationality of the "lung-spleen treatment" approach needs to be established through bidirectional verification of clinical efficacy and mechanistic studies. At the clinical level, Luo Xuehua et al. found that the method of invigorating the spleen and benefiting the lung can stabilize TCM syndrome scores; Zheng Yu's team further confirmed that it can reduce the monthly decline rate of ALSFRS-R to 0.64–0.66 points (significantly lower than the 1 point/month in the natural course of the disease), especially improving bulbar symptoms and quality of life (P<0.05) [1;5-6] . More notably, the respiratory protection effect has become a key breakthrough: the combination of spleen-invigorating and lung-benefiting prescriptions with BIPAP ventilators shortens the duration of ventilator dependence, and acupoint application synergistically increases FVC%, MIP, and MEP (P<0.05), suggesting that the concurrent treatment of lung and spleen has a direct physiological effect on the consolidation of Zongqi [13-14] .

The biological basis of this clinical efficacy is explained in the mechanistic research by Pan Xianmei et al.: the spleen-invigorating and lung-benefiting prescription forms an "anti-inflammatory- neuroprotective" cascade by inhibiting p38 MAPK phosphorylation → blocking microglial activation → down-regulating the expression of TNF-α and COX-2 (P<0.01) [7] . This mechanism perfectly echoes the TCM theory of "consolidating Weiqi" — Weiqi dysfunction leads to immune hyperactivity, while invigorating the spleen and benefiting the lung reestablishes immune balance by regulating inflammatory pathways, providing a complete evidence chain from clinical phenomena to molecular mechanisms for the concurrent treatment of lung and spleen.

3. Spleen-Kidney Emphasis: Mechanistic Leap from Theoretical Deepening to Yuanqi Protection

As ALS progresses to the middle and advanced stages, the limitations of merely lung-spleen treatment become evident, prompting the theoretical deepening toward "simultaneous treatment of spleen and kidney". Gu Xizhen and Wu Feifei et al. pointed out that the spleen, which governs muscles, serves as the foundation of postnatal (acquired) constitution, while the kidney, which stores essence, acts as the source of congenital (inborn) constitution; both are responsible for

nourishing muscles and bones [10;8] . Liao Weilong et al. further emphasized that "spleen deficiency leads to muscle atrophy, and kidney deficiency results in Yuanqi decline", revealing that Yuanqi exhaustion is the internal driving force behind the accelerated apoptosis of neurons [11] . This theoretical evolution has received crucial support from the mechanistic research by Zhu Wei et al.: the spleen-invigorating and kidney-tonifying formula protects mitochondrial function by activating PINK1/Parkin-mediated mitophagy, thereby increasing the number of anterior horn neurons in the spinal cord ($P<0.05$) and significantly improving the motor balance ability of ADAR2 mice [9] .

This finding transforms "preserving Yuanqi" from an abstract concept into a verifiable biological pathway: Yuanqi decline corresponds to mitochondrial energy crisis, and kidney-tonifying and essence-filling drugs delay neuronal degeneration by maintaining mitochondrial homeostasis, forming a closed loop of "theoretical hypothesis - mechanism verification - efficacy feedback". Essentially, this progression of therapeutic methods from lung-spleen to spleen-kidney is an accurate response to the evolution of ALS pathogenesis from "Zongqi dysfunction" to "Yuanqi decline".

4. Internal-External Combined Treatment: Meridian Synergistic Enhancement and Integration of Staged Intervention

Single internal decoctions are insufficient to address the multi-system damage in ALS, making internal-external combined treatment an inevitable choice for enhanced efficacy. Xu et al. confirmed that Du Meridian moxibustion (once weekly) combined with Western medicine significantly improved functional scores in ALS patients with spleen-kidney yang deficiency ($P<0.05$). Li et al. found that "Peitu Shengjin" (reinforcing earth to generate metal) acupoint application (Feishu, Pishu, Shenshu) synergized with "Jianpi Yifei" decoction, increasing the total effective rate to 88.46% ($P<0.05$) [15;13] . The underlying logic for these efficacy breakthroughs lies in: external treatments amplify the effects of internal decoctions through the meridian system – Du Meridian moxibustion warms and unites primordial yang to consolidate the prenatal foundation, while acupoint application reinforces earth to generate metal, strengthening the postnatal source, forming a multi-dimensional "medicine-acupoint-meridian" regulatory network.

Based on the spatiotemporal patterns of pathogenic evolution and therapeutic response, a three-qi staged intervention framework is proposed: To operationalize the above three-stage strategy, a concise protocol is summarized in Table 1, which aligns each disease stage with its corresponding TCM pathogenesis, therapeutic principle, and combined internal–external treatment.

Table 1 Three-Qi staged intervention framework for als

Protocol	Zongqi sinking	Treatment Principle	Treatment Method
Early	Zongqi sinking	Fortify Zongqi to stabilize respiratory axis	"Jianpi Yifei" decoction + Du Meridian moxibustion (Dazhui-Zhiyang)
Mid-stage	Weiqi dysfunction	Reinforce Weiqi to suppress immune axis	"Jianpi Yifei" decoction + acupoint application
Late-stage	Yuanqi collapse	Consolidate Yuanqi to protect energy axis	"Jianpi Bushen" decoction + Du Meridian moxibustion (Mingmen-Yaoyangguan)

This framework integrates scattered clinical evidence into a dynamic intervention pathway, reflecting precise matching of "pathogenesis-therapy-stage".

5. Research Gaps and Future Directions

Current research exhibits three major limitations:

1) Stratification Deficiency: Most studies lack stratification by disease stage, leading to

mismatches between intervention timing and pathogenesis [1-7; 12-14] .

2) Mechanistic Disconnection: Animal models focus on p38 MAPK [7] and PINK1/Parkin [9] , but clinical studies lack concurrent biomarker validation (e.g., IL-6, 8-OHdG).

3) Blinding Deficiencies: Only 2 studies employed sham moxibustion controls, making placebo effects difficult to exclude [15] .

Future research should validate the long-term benefits of staged intervention through multicenter RCTs integrating "function-structure-molecule" three-dimensional assessments (ALSFRS-R, cervical DTI-FA values, serum inflammatory factors).

6. Conclusion

The "Zongqi-Weiqi-Yuanqi" progressive theory systematically elucidates the pathogenic evolution of ALS from respiratory muscle involvement to systemic energy failure. "Jianpi Yifei" therapy protects neurons through anti-inflammatory effects, "Jianpi Bushen" therapy delays degeneration via mitophagy, and internal-external combined treatments achieve synergistic enhancement through meridian regulation. The staged intervention strategy constructed herein provides a clinically actionable pathway for precise TCM treatment of ALS, urgently requiring validation through high-quality studies.

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