

Research Progress of Acupuncture and Moxibustion in the Treatment of Amyotrophic Lateral Sclerosis

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurological lesion characterized by simultaneous involvement of upper and lower motor neurons, selective and progressive degeneration, leading to progressive paralysis and death, and is one of the most difficult diseases in the world. So far, there are only a handful of drugs for the treatment of ALS. Acupuncture has achieved certain results in the field of ALS treatment, which can effectively alleviate the clinical symptoms of patients and improve their quality of life. The author summarizes the methods and related mechanisms of acupuncture treatment of ALS at home and abroad in recent years, in order to provide a theoretical basis for acupuncture treatment of ALS in the future.

Amyotrophic Lateral Sclerosis (ALS) is a neurological injury characterized by the simultaneous involvement of the upper and lower motor neurons, with selective and progressive degeneration. It is manifested as a potential and inevitable decline in upper, lower extremity and whole body motor function, accompanied by gradual impairment of muscle strength, physical coordination, swallowing function, and respiratory function, and eventually death. However, the sensory nerves at the lesion site were not violated, and there was no loss of memory and sensory function. The pathogenesis may be related to genetic mutation, excitatory amino acid toxicity, oxidative stress, infection and autoimmunity, neurotrophic factor deficiency, unbalanced distribution of heavy metal elements, environmental factors, apoptosis, viral infection and abnormal aggregation of neurofilaments. related to the reason.

1. Epidemiology

The prevalence of the disease is about (4.1~8.4)/100,000 people, and the incidence rate is (0.6~3.8)/100,000 people. The incidence of men is about 1-2 times that of women, the average age of onset is 51 to 66 years old, and the average survival time from the onset of the disease is 24 to 50 months[1]. Information released by international epidemiology pointed out that 1-2 cases of ALS

patients are newly added in 100,000 people every year, and the increase of age is proportional to the prevalence rate [2]. A forecast published abroad [3] shows that from 2015 By 2040, the prevalence of ALS cases will increase by nearly 30% between the ages of 20 and 40.

2. Current Status of ALS Treatment

So far, most western medicine treatment is based on symptomatic treatment. Riluzole and edaravone are FDA - approved drugs for the treatment of ALS, but they can only prolong the life of patients by less than half a year, not only can they not be terminated or Reversing the development of the disease is expensive and accompanied by adverse reactions such as nausea and fatigue. Based on this, whether we can start from the traditional medicine of the motherland and seek a new treatment entry point, we need to think further. TCM acupuncture, as one of the main treatment methods in TCM, has been proven to have advantages in the treatment of various diseases. Acupuncture and acupuncture based on syndrome differentiation and treatment are simple and quick to operate, economical, and effective. The advantages of acupuncture in the treatment of ALS can also be further improved. In recent years, some physicians have treated ALS through clinical research, combined with the theory of syndrome differentiation and treatment of traditional Chinese medicine, focusing on acupuncture and moxibustion, supplemented by traditional Chinese medicine, massage, rehabilitation and other treatment methods to treat ALS, and achieved certain curative effects. The author summarizes the related research on acupuncture treatment of ALS at home and abroad in recent years, and analyzes its clinical efficacy and mechanism, in order to put forward a new understanding of the treatment of ALS, and provide a theoretical basis for further clinical research and clinical treatment of ALS.

3. The Concept of Traditional Chinese Medicine for ALS

There is no disease name for "Amyotrophic Lateral Sclerosis" in Chinese medical literature. Due to the numerous clinical manifestations of the disease ALS, ancient and modern physicians included it in the categories of "atrophy syndrome, wind prickly heat, rash syndrome, and tremor syndrome" to discuss and treat it. However, as far as the clinical manifestations of ALS are concerned, muscle weakness, muscle atrophy and motor dysfunction are dominant, so most physicians classify the disease as "atrophy syndrome" in traditional Chinese medicine.

"Neijing" is the earliest monograph to record atrophy syndrome, and it discusses the atrophy syndrome in detail. "Su Wen • Atrophy Theory" records the "five zang atrophy", including liver, heart, lung, spleen, kidney and other viscera. Lesions, its etiology and disease mechanism can be summarized in the following aspects: diet imbalance, emotional abnormalities, overwork and so on. At the same time, the "Nei Jing" also discusses various clinical manifestations of atrophy, such as: "If the kidney qi is hot, the lumbar spine will not lift, the bones will dry up and the marrow will be reduced, resulting in bone atrophy" [4]. Modern physicians further study on the basis of predecessors, discussing that the disease is mostly demonstrated from the viscera, which is closely related to the lung, spleen, liver, and kidney. It is common for multiple viscera to occur at the same time, and it is combined with the meridians. False syndromes are the main ones, and many false and real ones are mixed together.

To sum up, ALS belongs to the category of "impotence disease" in traditional Chinese medicine, and it is mainly treated from the three organs of liver, spleen and kidney.

4. TCM Acupuncture Treatment of ALS

The etiology and pathogenesis of ALS are still unclear. Traditional Chinese medicine believes

that the pathogenesis of atrophy is related to internal and external factors, and a combination of multiple pathogenic factors occurs in this disease, which affects the spleen and stomach, and causes liver and kidney yin deficiency for a long time. Stasis. Therefore, in the treatment, attention should be paid to the acquired benefits. Acupuncture, as a unique therapy of traditional Chinese medicine, has special advantages : simple acupoint selection, economical and safe, and obvious effect. It is also the most commonly used treatment method for ALS patients. "Plain Questions, Atrophy Syndrome" "replenishing the ying and opening the shu, adjusting the deficiency and excess, and harmonizing the inversion" is an important principle of acupuncture and moxibustion in the treatment of atrophy. Focusing on the treatment of the liver, spleen, and kidney, the Yangming meridian with more qi and blood is the main point, supplemented by the acupoints on the two meridians of Taiyang, Shaoyang and the Du meridian, and according to different situations, the principle of syndrome differentiation and treatment is flexibly applied, combined with symptomatic treatment, according to the different constitution of the patient, the benefit is also different, the doctor treats ALS based on this, and obtained satisfactory curative effect.

5. Acupuncture Methods for ALS

5.1. Acupuncture Treatment

Huaiming[5] and others advocated that the disease is caused by deficiency of liver and kidney and insufficient essence, and the principle of treatment is to nourish the kidney and nourish the liver, and nourish the essence and fill the marrow. Acupuncture was performed on 20 ALS patients, and the main points were Fengfu and Huatuojiaji, among which Jialianquan and Yifeng were accompanied by dysarthria. Operation: Fengfu, lower the head to select acupoints, use a 0.30 mm diameter needle to stab obliquely in the direction of the lower collar, the bird pecks into the needle 60-75mm, and the needle is immediately released when there is an electric shock-like feeling all over the body and the body shakes involuntarily; Fengchi: Needle 35-60mm in the direction of the Adam's apple, with the degree of distention in the throat and twitching of the contralateral or ipsilateral upper limb as the degree, the needle is withdrawn immediately; Huatuo Jiaji: open 5 minutes from the side of the spine, puncture 25-38mm straight, and twist and twist together Replenishing and reducing for 1-2 minutes; Yinfeng: obliquely puncturing 38-62 in the direction of the throat, applying twisting, turning and reducing method for 1 minute; 1-2 times a day, 3 months as a course of treatment. After 1 to 4 courses of treatment, the effective rate is 85%.

Zhao Lijie et al [6] used warm acupuncture and moxibustion to treat 10 cases of ALS patients and observed the curative effect, mainly selected the Yangming meridian points such as the shoulder bone, Shouwuli, Quchi, Shousanli, Hegu, lower limbs: Liangqiu, Zusanli, Shang Juxu, Jiexi and other points, Beishu points such as Feishu, Xinshu, Ganshu, Pishu, Shenshu, etc. are acupuncture, and the total effective rate is 70% for 3-6 courses of treatment. Neuronal disease can play the role of warming the spleen, invigorating the kidney and nourishing the liver, strengthening the muscles and strengthening the power to relieve atrophy, and the clinical effect is satisfactory.

Li Ling et al. [7] used the theory of "to treat atrophy by taking Yangming alone", and acupuncture at acupoints of the Yangming meridian in the treatment of 4 patients with familial amyotrophic lateral sclerosis., Zusanli, Jiexi, operation: Hegu, Zusanli use the tonic method (twist), and the rest of the acupoints are filled and reduced. One treatment per day, 30min per treatment, 1 acupuncture every 10min, 2 acupuncture sessions in total during needle retention; 10 consecutive treatments as one course of treatment, 2 days rest between courses for the next course of treatment, a total of 3 courses of treatment. Subjects were placed in a supine or sitting position. The changes of nerve conduction and electromyography and clinical manifestations of the patients before and after

treatment were observed. During the treatment, attention was paid to emotional evacuation and functional enhancement. The results confirmed that acupuncture can delay the development of the disease and obtain a good curative effect.

5.2. Combined Application of Acupuncture and Moxibustion

Wang Yan [8] used abdominal acupuncture as the main therapy, combined with Shenque point moxibustion in the treatment of 1 case of ALS patients, and the curative effect was good. The internal organs of the human body are distributed in the abdomen, including all the neurotransmitters of the central nervous system of the human body [9]. Abdominal acupuncture is a method of treating systemic diseases through acupuncture at specific acupoints in the abdomen to adjust the yin and yang of the qi machine and realize the dynamic balance of the yin and yang of the human body. A new type of acupuncture therapy. Take Zhongwan, Guanyuan, Xiawan, Qihai, Huaroumen, Wailing, Daheng, Shangfengshi point, Shangfengshi point, Shangfengshiwai point, Xiafengshi point, Xiafengshi point (both sides). Zhongwan, Guanyuan, lower abdominal, thorn to the deep layer of adipose tissue, above the muscle layer, sliding meat door, outer ling, Daheng, upper rheumatic point, upper rheumatic upper point, upper rheumatic outer point, lower rheumatic point, lower rheumatic point Shallow acupuncture at the lower point, the depth of which is located in the superficial layer of the subcutaneous fat layer. All points are only twisted and inserted without lifting, and there is no need to feel deqi. After the needle is inserted, stay for 3 to 5 minutes, and then twist again after 3 to 5 minutes to cause local generation. Needle feeling, acupuncture every 5 minutes to strengthen the needle feeling to spread to the surrounding or distant place, keep the needle for 30 minutes and start the needle, moxibustion smoked and moxibustion at Shenque point when the needle is kept, once a day, 7 days as a course of treatment, a total of 3 a course of treatment.

Guan Sumei et al. [10] mainly treated acupuncture, combined with acupoint injection and intravenous injection, and the curative effect was good in 1 case. The patient in this case is a type of deficiency of liver and kidney, and the treatment is to nourish liver and kidney, nourish blood and soften tendons. First, acupuncture points T1-T8 Jiaji, Ganshu, Pishu, Weishu, Shenshu, Zhibian and Weishu were taken in the prone position. China and Kunlun. 0.30mm×75mm filigree needles were used to puncture 2~2.5cun in Zhibian, 0.30mm×40mm filigree needles were used for the remaining points, and Jiaji, Ganshu, Pishu and Weishu points were punctured obliquely 0.5~0.8cun toward the spine. Shenshu, Weizhong, and Kunlun points are directly punctured 0.8-1.5cun. After getting qi in Zhibian and Weizhong, the method of lifting, inserting and removing the qi is performed, and the lower limbs are twitching as the degree. The Jiaji point was treated with the method of leveling, supplementing, leveling and reducing, and the needles were retained for 20 min. In the supine position, 0.30mm×40mm filigree needles were used for routine acupuncture on both sides of Quchi, Hegu, Qihai, Guanyuan, Zusanli, Yanglingquan, Liangqiu, Fenglong, Sanyinjiao, Taixi, and Taichong. Hai, Guanyuan, Zusanli, Sanyinjiao, Taixi, and Taichong acupoints were swirl and supplemented after obtaining Qi, and the remaining points were stabbed 1-1.5 cun straight, and the needles were retained for 20 minutes. Acupuncture once a day. Intravenous injection of Shenjie, 1 time a day, 7 times as a course of treatment; Zusanli acupoint injection of mecobalamin 1 mL each time, once a day, alternating left and right, 7 times as a course of treatment. After 4 courses of treatment, the muscle strength of the limbs was V, the hypertonia was weakened, the patient could walk slowly on his own, the feeling of weakness in the limbs was relieved, the tension in the left lower limb disappeared, and the gag reflex was weakened. The patient felt better and satisfied with the treatment effect. Although there are few reports of such cases and lack of sufficient clinical cases for our study, it also provides a better idea for the clinical treatment of ALS.

5.3. Combined Application of Acupuncture and Medicine

Chen Xiao et al. [11] took "strengthening the spleen and strengthening the muscles, nourishing the kidneys and strengthening the tendons, and nourishing the liver and relieving tremors" as the treatment method. Acupoint selection for acupoint injection: Neiguan and Zusanli. Drug [3]: Astragalus injection. Operation method: Use a 2ml disposable syringe to extract 2 mL of the drug for use; take bilateral acupoints (Neiguan or Zusanli) to disinfect the skin, insert the needle of the syringe according to the acupuncture technique and requirements, and lift and insert or twist it to the acupoint to obtain qi., the syringe was withdrawn and no blood was drawn; the patient was instructed to relax and do a quick swallowing exercise; the patient did a quick swallowing exercise and quickly injected about 1ml of liquid medicine into the acupoint, and pressed an appropriate amount at the injection site; after the injection, the acupoint was pressed for 2-3 minutes Symptoms disappear. Do the same for the other side. The above two groups of acupoints were used alternately, 1 time for 1d -1, and 10 times as a course of treatment. The moxibustion sources are: Governor Vessel on the back and Taiyang Bladder Meridian on both sides. Operation: Moxibustion with moxa sticks, select the main points of the Du meridian, such as Baihui, Dazhui, Jizhong, Mingmen, Yaoyangguan and Beishu points on the bladder meridian, to make the local skin flush, once every other day, 10 times Each time is 1 course of treatment. It is confirmed that the comprehensive program of traditional Chinese and western medicine has obvious advantages in the treatment of amyotrophic lateral sclerosis compared with the single use of western medicine.

Xiong Zuoling et al [12] believed that ALS was caused by deficiency of liver, spleen and kidney, internal movement of liver wind, and phlegm obstructing collaterals. 6 cases of "amyotrophic lateral sclerosis" were treated with traditional Chinese medicine decoction to calm the liver and eliminate wind, nourish the kidney, invigorate the liver and invigorate the spleen, activate blood and dispel phlegm and clear the collaterals, combined with acupuncture and rehabilitation training. Sanli, Hegu, Jiaguan, Liangqiu, Zusanli, and Xiexi. Acupuncture and moxibustion were performed once every other day, 20 minutes of waking up, Huatuo Jiaji beating with plum blossom needles for 10 minutes, and cupping of Beishu for 5 minutes. Acupuncture and moxibustion are mainly based on acupoints selected from the Yangming meridian, to nourish qi and blood, and to moisten the tendons; Huatuo Jiaji is beaten with plum blossom needles, and cupping is performed on the back. Observing the control of each case before and after treatment, the condition of each case was well controlled, and the muscle strength was recovered, and the life was basically self-care.

Meng Bin et al [13] conducted a cohort study on 28 ALS patients, and randomly divided them into 15 treatment groups and 13 control groups. The treatment group was treated with " Tongdu Wenyang " acupuncture combined with riluzole, and the control group was treated with riluzole. The group was only treated with riluzole, and its clinical efficacy was observed. Take the Governor Meridian Points: Yaoshu, Yaoyangguan, Mingmen, Jizhong, Central, Tendon Shrinkage, Zhiyang, Lingtai, Shendao, Body Column, Taodao, Dazhui, Baihui, Shenting. Acupuncture at Mingmen and Yaoyangguan for 1.0 to 1.5 cun, and then acupuncture with a small degree of twisting acupuncture for 1 minute; At Yaoshu point, the needle tip and the skin are at an angle of about 80° , and the needle point is slightly inclined upward for about 0.8-1.0 cun. After the acupuncture is depleted of Qi, each acupuncture point is individually twisted for 10 s; the Baihui needle point is 15-20° to the skin The angle is rapidly pierced into the subglacial aponeurosis by about 0.5 to 1.0 cun in the direction of the forward Shencong, and then a slight twisting manipulation is performed for 1 minute; The lower layer of the membrane is about 0.3 to 0.5 cun, and after deqi, a small-scale twisting manipulation is performed for 1 minute; the needles are kept for 30 minutes after acupuncture at each point after deqi. 1 time a day, 2 months as a course of treatment, a total of 3 courses of treatment. The results showed that after 6 months of treatment of ALS patients with

"Tongdu Wenyang" acupuncture combined with riluzole tablets, the scores of TCM syndromes of atrophy and Appel function scale decreased to varying degrees, and the scores in the treatment group decreased more than those in the control group. The difference was statistically significant, suggesting that "Tongdu Wenyang" acupuncture combined with riluzole tablets can delay the progression of ALS and improve the quality of life to a certain extent.

Sun Jun [14] and others believed that bee acupuncture could activate blood and warm meridians, remove dampness and phlegm, detoxify and relieve pain, and proposed to use bee acupuncture as the main treatment for ALS, supplemented by traditional Chinese medicine decoction and exercise. First of all, for the sake of safety, a skin test should be performed. Take one Quchi or Zusanli point. After local disinfection, take a bee and stab the acupoint directly, squeeze the poison sac, and then pull out the bee needle. After 15 minutes, observe that there is no body. Adverse reactions or other discomfort can be treated. Take Huatuo Jiaji acupoints and Du meridian acupoints as the main acupoints, and can be used with Ganshu, Pishu, Shenshu, Dachangshu, Fengchi, Tianzhu, Jianli, Quchi and Zusanli (both bilateral), Baihui, Fengfu, etc. Operation method: After acupuncture trial, treatment can be performed in stages. In the acute stage, frequent prickling is required. The sting needle of the live bee is directly inserted into the selected part, and the needle is kept for 10 to 20 minutes and then pulled out. Generally, one bee and one acupoint are selected at the beginning, and only 1~2 acupoints are selected at the beginning, and the number of acupoints is gradually increased according to the specific situation of the patient, usually no more than 20. If the limbs are weak and the muscle atrophy is severe, acupuncture can be given 1~2 times a day; patients with milder condition can be treated once every other day, 10 times as a course of treatment, and the interval between courses of treatment is 3~4 days. The specific number of courses of treatment is better to maintain 1-2 courses of treatment after the acute attack is controlled. In remission, the treatment interval can be gradually extended. After the article, an actual case was used to verify the curative effect. After receiving a one-month treatment, the patient's cough and facial muscle tremors disappeared. After three months of treatment, the scope of muscle atrophy was reduced, the body weight was increased by 7 kg, and the muscle strength was enhanced, and the condition was stable., can carry out daily activities independently. It provides another therapeutic idea for clinical treatment of ALS.

6. The Mechanism of Action of Acupuncture in the Treatment of ALS

6.1 Effects of Acupuncture on Glutamate Toxicity

Glutamate excitotoxicity can lead to motor neuron death, which is one of the most important hypotheses in the pathogenesis of ALS. So far, the only effective therapeutic target approved by the US FDA is anti-glutamate excitotoxicity. Sun Yuanzheng et al. [15] confirmed through experimental studies that Jiaji electroacupuncture can reduce the level of glutamate in the neuronal microenvironment by up-regulating the expression of EAAT2 in the lumbar spinal cord of SOD1 G93A transgenic mice, and at the same time by up-regulating the expression of AMPA receptor GluR2 subunit in the lumbar spinal cord. expression, and improve the ability of neurons to resist excitotoxicity. Therefore, acupuncture can improve the symptoms and prolong the survival time of ALS patients by anti-glutamate excitotoxicity.

6.2 Effects of Acupuncture on Oxidative Stress

Oxidative stress (OS) refers to that when the body is subjected to harmful stimuli, a large number of reactive oxygen species (ROS) are produced, and the degree of oxidation exceeds the scavenging ability of oxides, resulting in an imbalance between oxidation and anti-oxidation in the body.

Previous ALS autopsy and experimental studies have found that oxidative stress biomarkers in the cerebrospinal fluid, plasma and urine of ALS patients were significantly elevated [16]. In ALS patients, mitochondrial dysfunction and oxidative stress form a vicious cycle that promotes neurodegeneration and muscle atrophy. Guo Jing [17] conducted electro-acupuncture at L1-2 and L5-6 Jiaji points on both sides of ALS model mice, and confirmed that electro-acupuncture at Jiaji points can down-regulate COX-2 expression, thereby reducing the oxidative stress damage of nerve cells and exerting a protective effect on nerves.

6.3 Effects of Acupuncture on Neuroinflammatory Response

There are obvious inflammatory manifestations in the pathogenesis of ALS [18]. Microglia are the innate immune cells of the nervous system and are activated in all ALS cases, with astrocytes in early onset and microglia in late stages [19]. Wei Yan et al. [20] applied Jiaji electroacupuncture to intervene in ALS-SOD1 G93A transgenic mice, and observed that the expression of P-P38 in the anterior horn motor neurons of the lumbar spinal cord of the transgenic mice was down-regulated, the activation of P38 MAPK was inhibited, and the neuronal cells were affected. effective protection. This study revealed that Jiaji electroacupuncture exerts a protective effect on neuronal cells against neuroinflammation and apoptosis. He Yunhan et al. [21] based on the treatment principle of "to treat atrophy by taking Yangming alone", electroacupuncture at bilateral Tianshu and Zusanli points in SOD1 G93A model mice confirmed that early acupuncture intervention can reduce the pro-inflammatory factor TNF in the brainstem and spinal cord. -The release of alpha. Su Su et al [22] also showed that Jiaji electroacupuncture can protect the motor neurons in the anterior horn of the lumbar spinal cord by inhibiting the p38MAPK/NF- κ B signaling pathway, thereby alleviating the progression of ALS. The anti-neuroinflammatory mechanism of acupuncture in the treatment of ALS was discussed at the molecular level.

6.4 The Effect of Acupuncture on Autophagy

Autophagy is a life phenomenon that exists widely in eukaryotic cells. It is a mechanism for cells to maintain their own balance. On the one hand, it can remove pathogens, remove abnormal proteins and damaged cells; on the other hand, it regulates immune function and endocrine. The increased number of autophagosomes in ALS spinal cord tissue suggests that autophagy is activated during the pathogenesis of ALS. Therefore, increasing autophagy may be an effective target for the treatment of ALS. Guo Ying [23] used Jiaji electroacupuncture to treat ALS-SOD1 G93A transgenic mice. By up-regulating the expression of autophagy-related proteins LC3-II and Beclin1, it enhanced autophagy function, promoted the removal of abnormal proteins in cells, and played a protective role. The role of neurons, neuron loss, delays the onset of disease, and prolongs survival. It is suggested that Jiaji electroacupuncture can improve the function of ALS neurons by enhancing autophagy.

6.5 Effects of Acupuncture on Organ Inflammatory Response and Immunity

Research has shown that multiple organ dysfunction in ALS animals and patients, including inflammatory responses in the lung, spleen, liver, and kidney. In an ALS animal model, Lee SH et al. [24] applied bee acupuncture to reduce the levels of inflammatory proteins tumor necrosis factor (TNF)- α , Iba-1, and cyclooxygenase 2 (COX2) in the liver, spleen and spleen of transgenic mice. Inflammatory response of the kidneys. This study confirmed that bee acupuncture combined with acupuncture stimulation could prevent spinal motor neuron death and enhance anti-inflammatory effects in symptomatic hSOD1 G93A transgenic mice, and the effect was better than bee

acupuncture alone. Bee acupuncture treatment of Zusanli can enhance immune response and regulate immunity by reducing inflammatory proteins in the spleen of hSOD1 G93A transgenic mice.

7. Conclusions

To sum up, ALS is a rare and refractory disease, and there is still no effective drug. Traditional Chinese medicine can delay the development of the disease to a certain extent, improve clinical symptoms, and improve the quality of life of patients. As one of the important treatment methods, acupuncture and moxibustion use the "treatment of atrophy alone with Yangming", focusing on acupoints of the Yangming meridian of the hands and feet, combined with other methods such as moxibustion, rehabilitation training, and acupoint injection in clinical practice. Satisfactory curative effect has also been achieved in the application, but lack of a large number of clinical data, it has not been widely recognized. These are all difficulties that we need to overcome urgently. Therefore, in the future clinical process, we should collect as many cases as possible, adopt evidence-based medicine, increase multi-center, large-sample, randomized controlled clinical trials; carry out laboratory data research on acupuncture treatment of ALS, and establish acupuncture treatment for ALS. evidence-based medicine. At the same time, in the face of sudden serious illness, the patient is physically and mentally damaged, so we should pay more attention to the patient's mental and psychological condition and improve the quality of life of the patient. Although ALS has a high degree of malignancy in terms of prognosis, as a doctor, it is not easy to feel pessimistic. More and more effective treatment methods should be actively explored in the future clinical practice to further improve the clinical efficacy of this disease and the comfort of patients.

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