

Dihuang Yinzi, a Classical Chinese Herbal Prescription, for Amyotrophic Lateral Sclerosis: A 12-Year Follow-up Case Report

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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating progressive neurodegenerative disease with no effective treatment and death within 2 to 5 years after symptom onset. Here, we reported a case of ALS patient using modified Dihuang Yinzi (DHYZ), a classical traditional Chinese medicine (TCM) prescription, who has survived 12 years with significant improvement in bulbar paralysis.

A 41-year-old Chinese Han nationality woman was admitted to the hospital with complaints of weakened bilateral grip, slurred speech, stumbling, and muscle twitching for 3 years. The electromyography showed neurogenic injury in bilateral upper limbs and tongue. She was diagnosed with ALS according to the revised El escorial criteria. The patient was orally administrated with Riluzole 100 mg daily for 10 months and then stopped. Subsequently, she resorted to TCM. Based on the TCM theory, the patient was diagnosed with *Yinfei* syndrome because of kidney deficiency. DHYZ was chosen because it has the function of replenishing kidney essence to treat *Yinfei* syndrome. Up to now, she has been using modified DHYZ continuously for 12 years. The patient survived with ALS and did not require permanent continuous ventilator. In addition, the symptoms of choking on liquids are improved, and the utility of 30 mL water swallow test was improved

with grade 2. The symptoms of muscle fibrillations of limbs are also reduced. However, muscle strength worsened slowly. The repeated electromyography showed motor conduction amplitude reducing gradually and velocity not changing more when compared with the initial electromyography.

Our findings suggested that DHYZ can be potentially used in ALS patients because of its multi-targeted neuroprotection and general safety, although ALS does not have a cure. In addition, we identified the area that is worthy of further study and DHYZ as a promising candidate for further clinical application and ALS trials. Rigorous randomized controlled trials are needed in the future.

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Abbreviations: ALS = amyotrophic lateral sclerosis, CAM = complementary and/or alternative medicine, CHM = Chinese herbal medicines, DHYZ = Dihuang Yinzi, EMG = electromyography, MRI = magnetic resonance imaging, TCM = traditional Chinese medicine.

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by relentless loss of motor neuron function.¹ The selective degeneration of upper and lower motor neurons results in progressive weakness of the limb, bulbar, abdominal, and thoracic muscles. The reported annual prevalence and incidence rates of ALS were only 9.9 and 2.3 per 100,000 people per year respectively in Asian country, Japan.² However, the importance of ALS should not be underestimated since there are more than one in 500 people who will die of the disease in the industrialized world.³ Without mechanical ventilation, most patients die within 2 to 5 years after symptom onset because of respiratory failure, although 5% to 10% of patients may live more than 10 years.⁴ Up to now, riluzole was the only drug approved by the Food and Drug Administration as neuroprotective treatment/disease-modifying treatment for ALS that has been shown to slightly slow the course of ALS.⁵ Oral administration of riluzole 100 mg daily for ALS patients is reasonably safe and prolongs a limited lengthening of median survival by ~2 to 3 months after 18 months treatment.⁶ To our knowledge, other than riluzole, there are no other new treatment that can halt or reverse the progressive loss of neurons, leading to an increase of the ALS life expectancy. Given the fatalness of the illness and lack of effective neuroprotective treatment/disease-modifying agents, complementary and/or alternative medicine (CAM) is thus increasingly sought to treat ALS worldwide.⁷

Traditional Chinese Medicine (TCM) is a main form of CAM originating in ancient China and has been practiced for a history of 3000 years. Accordingly, Chinese herbal medicines

(CHMs) are frequently used in the treatment of ALS. Studies in vivo and in vitro showed that CHMs have a great potential for treatment of ALS, with neuroprotective function against excitatory amino acid toxicity, oxidative stress, calcium cytotoxicity, and neuroinflammation.⁸ During Song Dynasty (960–1279 AD), the TCM prescription book *Shengji zonglu* (*Complete Record of Sacred Benevolence*) compiled by Zhao Ji who was the eighth emperor of Song Dynasty of China in 1111 to 1117 AD. This book lists 20,000 TCM prescriptions and describes the causes, symptoms, and cures for different diseases. Dihuang Yinzi (DHYZ), a classical TCM prescription for neurological disorders *Yinfei* syndrome that centered on the symptoms of the speech and language disorders such as aphasia and logopathy (*Yin* syndrome) and disorders of motility such as motor paralysis and difficulty in walking (*Fei* syndrome), was first recorded in this book with the name Dihuang Yin. It is composed of 12 kinds of CHMs: (a) Radix Rehmanniae Preparata 15 g; prepared rehmannia root (Shudihuang), the dried roots of Radix Rehmanniae Recens; (b) Fructus Corni 15 g; asiatic cornelian cherry fruit (Shanzhuyu), the dried ripe pulp of *Cornus officinalis* Sieb. et Zucc.; (c) Herba Cistanches 15 g; desertliving cistanche (Rousongrong), the dried roots of *Cistanche deserticola* Y. C. Ma; (d) Radix Morindae Officinalis 15 g; morinda root (Bajitian), the dried roots of *Morinda officinalis* How.; (e) Radix Aconiti Lateralis Preparata 15 g; prepared common monkshood branched root (Fuzi), the processed root of *Aconitum carmichaeli* Debx.; (f) Cortex Cinnamomi 15 g; cassia bark (Rougui), the dried bark of *Cinnamomum cassia* Presl; (g) Herba Dendrobii 15 g; dendrobium (Shihu), the dried roots of *Dendrobium loddigesii* Rolfe. or *Dendrobium fimbriatum* Hook. var. *oculatum* Hook. or *Dendrobium chrysanthum* Wall. or *Dendrobium officinale* Kimra et Migo or *Dendrobium nobile* Lindl.; (h) Radix Ophiopogonis 15 g; dwarf lilyturf tuber (Maidong), the dried roots of *Ophiopogon japonicus* (Thunb.) Ker-Gawl.; (i) Fructus *Schisandrae chinensis* 15 g; Chinese magnoliavine fruit (Wuweizi), the dried ripe fruit of *S. chinensis* (Turcz.) Baill.; (j) Rhizoma Acori Tatarinowii 15 g; grassleaf sweetflag rhizome (Shichangpu), the dried roots of *Acorus tatarinowii* Schott.; (k) Radix Polygalae 15 g; milkwort root (Yuanzhi), the dried roots of *Polygala tenuifolia* Willd. or *Polygala sibirica* L.; (l) Poria; Indian bread (Fuling) 15 g, the dried sclerotia of *Poria cocos* (Schw.) Wolf. (Table 1). In modern times, DHYZ is still used continuously and widely for treatment of neurological disorders such as stroke,⁹ Parkinson disease dementia,¹⁰ and spinal cord injury.¹¹ Here, we reported a case of ALS patient using modified DHYZ who has survived 12 years with significant improvement in bulbar paralysis.

CONSENT

Written informed consent was obtained from the patient before and after all procedures.

CASE PRESENTATION

Patient Information and Clinical Findings

On 31 July 2004, a 41-year-old Chinese Han nationality woman was admitted to the hospital with complaints of weakened bilateral grip, slurred speech, stumbling, and muscular twitchings for 3 years. The initial symptom, the intermittent weakness of right upper limb without numbness and pain, appeared in November 2001. The laryngological examination was normal. The magnetic resonance imaging (MRI) of head

and cervical vertebrae were negative. After 6 months, uncontrollable twitching was observed in the right upper limb and the patient's speech became slurred. On 5 March 2002, the electromyography (EMG) done at the Huashan Hospital affiliated to Fudan University showed neurogenic injury in bilateral upper limbs and tongue (Table 2). Based on the revised El escorial criteria,¹² clinically ALS was diagnosed. The patient was orally administrated with riluzole (50 mg, twice a day) for 10 months. She stopped the riluzole by herself because symptoms continuously deteriorated and could not bear the economic burden. On 31 July 2004, she was admitted to the hospital with weakness of limbs, dysarthria, dysphagia, and the clumsiness in daily activities. On examination, the four main vital signs, temperature, heart rate, blood pressure, and respiratory rate, were normal. The patient was alert with normal mental status. Cranial nerves examination showed the tongue muscle atrophy and tongue fasciculations. Motor system examination showed widespread muscle wasting and fasciculation of the bilateral thenar and interosseous muscles. Strength in the distal muscle of the upper bilateral limbs was of grade 2/5 to 3/5 and muscle strength in the lower bilateral limbs was of grade 3/5 to 4/5, graded on the Medical Research Council Muscle Strength Grading System.¹³ The sensory system was intact. Tendon reflexes were decreased with bilateral biceps, triceps, and brachioradialis. There were brisk reflexes of knee tendon and achilles tendon. The bilateral Hoffman signs were present, whereas the bilateral Babinski signs were not present. The utility of 30 mL water swallow test was grade 4. The laboratory blood test was generally normal. Her past drug history was not momentous except for the riluzole. The patient did not have the tobacco and alcohol consumption. She does not have a family history of ALS. TCM symptoms and signs were summarized as follows: sluggish speech, faint low voice, choke when drinking, weakness of limbs, muscle wasting of hands, muscular twitchings of upper limbs, pale facial complexion, soreness and weakness of waist and knees, excessive phlegm and saliva, constipation once every 3 days, pink tongue quality, tongue muscle atrophy and fibrillation, deep weak and thready pulse.

Diagnostic Assessment

The patient is a middle-aged woman. With muscles atrophy and fasciculations, the onset symptom is insidiously developing asymmetric upper limb weakness and then bulbar muscle. The clinical features are accompanied with the pathological signs: overactive tendon reflexes and clonus. The sensory system was intact. EMG studies showed typically neurogenic abnormalities. Based on the revisited El escorial criteria, she was diagnosed with clinically definite ALS, depending on the clinical manifestations and consistent electrodiagnostic studies. The clinical signs of myasthenia and muscular atrophy belong to *Fei* syndrome in TCM. When the patient experienced bulbar paralysis with symptoms such as dysarthria and dysphagia, the clinical features were classified to *Yin* syndrome in TCM. The kidney meridian dominates feet, throat, and tongue according to meridian theory of TCM. Thus, the kidney deficiency leads to *Yinfei* syndrome affecting both bulbar muscles and limbs muscles. Following the TCM theory, the patient was diagnosed with *Yinfei* syndrome because of kidney deficiency.

Therapeutic Intervention

Once the patient was diagnosed with ALS firstly in 2002, she was started on riluzole (50 mg, twice a day) for 10 months. When she noted that the treatment cannot arrest the disease

TABLE 1. Overview of Dihuang Yinzi

Chinese Name	English Name	Latin Name	Family	Dosage (g)	Prescription functions	Pharmacological functions of each herb
Shudihuang	Prepared rehmannia root	Radix Rehmanniae Preparata	The dried roots of Radix Rehmanniae Recens	15	Nourishing kidney yin	Rehmannia root and Catalpol have antioxidant, antiapoptosis, antiinflammation, and other neuroprotective properties and act in neurodegenerative diseases ^{25,26}
Shanzhuyu	Asiatic comelian cherry fruit	Fructus Corni	The dried ripe pulp of <i>Cornus officinalis</i> Sieb. et Zucc.	15		<i>p</i> -coumaric acid, ursolic acid, and gallic acid exerted antioxidant, antiapoptosis, and antineuroinflammation against Aβ-induced toxicity ^{27,28}
Rousongro ng	Desertliving cistanche	Herba Cistanches	The dried roots of <i>Cistanche deserticola</i> Y. C. Ma	15	Warming and recuperating kidney yang	Herba Cistanches and its active components possess neuroprotective function, hormone regulation, immunomodulatory, antioxidative, antiapoptotic, and antiinflammatory activities, making them potential treatment for various neurodegenerative disorders ²⁹
Bajitian	Morinda root	Radix Morindae Officinalis	The dried roots of <i>Morinda officinalis</i> How.	15		β-D-fructofuranosyl (2–2) β-D-fructofuranosyl enhanced antioxidative activity, antiapoptotic activity, and energy metabolism against Aβ-induced neurotoxicity ³⁰
Fuzi	Prepared common monkshood branched root	Radix Aconiti Lateralis Preparata	The processed root of <i>Aconitum carmichaeli</i> Debx.	15	Warming and nourishing lower energizer, controlling hyperactivity of yang, conducting fire back to its origin	Fuzi polysaccharide-1 affected brain-derived neurotrophic factor signaling pathways in the hippocampus ³¹
Rougui	Cassia bark	Cortex Cinnamomi	The dried bark of <i>Cinnamomum cassia</i> Presl	15		Cortex Cinnamomi has a neuroprotective effect on glutamate-induced neuronal death through the inhibition of Ca ²⁺ influx; ³² 2'-hydroxycinnamaldehyde has antineuroinflammatory and neuroprotective effects in the central nervous system by targeting lipoprotein receptor-related protein 1 ³³

Chinese Name	English Name	Latin Name	Family	Dosage (g)	Prescription functions	Pharmacological functions of each herb
Shihu	Dendrobium	Herba Dendrobii	The dried roots of <i>D. loddigesii</i> Rolfe, or <i>D. fimbriatum</i> Hook. var. <i>oculatum</i> Hook. or <i>D. chrysanthum</i> Wall. or <i>Dendrobium officinale</i> Kimra et Migo. or <i>D. nobile</i> Lindl.	15	Nourishing lung and kidney, mutual generation between metal and water, strengthening governor of water for coordinating fire	Its active compound and Chrysoxine exhibit antioxidant, antiapoptosis, and neuroprotective activities against neurotoxin-induced cell death. ^{34,35}
Maidong	Dwarf lilyturf tuber	Radix Ophiopogonis	The dried roots of <i>O. japonicus</i> (Thunb.) Ker-Gawl.	15		<i>O. japonicus</i> display antiinflammatory, antioxidative, and immunomodulative activities. ³⁶
Wuweizi	Chinese magnolia vine fruit	Fructus Schisandrae Chinensis	The dried ripe fruit of <i>S. chinensis</i> (Turez.) Baill.	15		Schisantherin A, schisandrin B, and schisandrin C attenuate abnormal oxidative stress and modulate the apoptotic signal pathway, exhibiting their neuroprotective function on neurodegenerative diseases. ^{37,38}
Shichangpu	Grassleaf sweetflag rhizome	Rhizoma Acori Tatarinowii	The dried roots of <i>A. tatarinowii</i> Schott.	15	Resolving phlegm for resuscitation, restoring coordination between heart and kidney	β -Asarone and eugenol have neuroprotective function cells through inhibiting apoptosis against A β -induced neurotoxicity. ³⁹
Yuanzhi	Milkwort root	Radix Polygalae	The dried roots of <i>P. tenuifolia</i> Willd. or <i>P. sibirica</i> L.	15		Polygalae radix has neuroprotective effects against toxin-induced neuronal death through its antioxidant and antiapoptotic activities; ⁴⁰ its ethanol extracts as a novel autophagy inducer modulate neurodegenerative disorders via reducing toxicity and clearing of mutant proteins in the cellular level. ⁴¹
Fuling	Indian bread	Poria	The dried sclerotia of <i>P. cocos</i> (Schw.) Wolf	15		<i>P. cocos</i> water extract has neuroprotective action against A β -induced neuronal injury through suppressing the oxidative stress and the apoptosis. ⁴²

TABLE 2. The Electromyography Examination

Study	Initial (3/5/2002)						Repeated (1/7/2014)						
	Right			left			Right			left			
Motor	Nerve	DML (ms)	AMP (mv)	CV (m/s)	DML (ms)	AMP (mv)	CV (m/s)	DML (ms)	AMP (mv)	CV (m/s)	DML (ms)	AMP (mv)	CV (m/s)
	Median	4.9	2.2	39.6	3.3	4.6	56.5	6.5	0.06	55	5.7	0.033	35
	Ulnar	2.8	6.2	52.6				2.7	0.726	58	5.7	0.906	45
Sensory	Peroneal							5.5	2.448	41	5.6	0.906	45
	Tibial							5.9	6.940	45	4.7	12.73	44
	Median	2.1	44	58.1				2.6	14.6	54	3.0	15.4	45
EMG	Ulnar	1.8	20	53				2.2	6.7	51	2.6	5.9	38
	Peroneal							2.5	5.7	42	2.0	6.1	45
	Sural							3.1	7.3	48	3.3	11.7	47
Muscle	Fibs	wave	Fasc	Fibs	wave	Fasc	Fibs	Fibs	wave	Fasc	Fibs	wave	Fasc
1st dorsalinter-osseous	2+	2+	None	1+	1+	None	None	1+	3+	3+	3+	3+	None
Tongue	1+	1+	None	None	None	None	None	None	None	None	None	None	Few
biceps brachii	None	None	None	None	None	None	None	None	None	None	3+	3+	None
Tibialis anterior	None	None	None	None	None	None	None	None	None	None	3+	2+	Many
vastus medialis	None	None	None	None	None	None	None	None	1+	None	None	None	None
Sternocleid-omastoid	None	None	None	None	None	None	None	None	None	None	None	None	None

EMG = electromyography.

condition and she cannot bear the economic burden, the patient discontinued treatment because riluzole is not a cure for ALS. In that time, she resorted to the TCM. Modified DHYZ was chosen because it has the function of replenishing kidney essence to treat *Yinfei* syndrome. The compositions and dosage of modified DHYZ are as follows: (a) Radix Rehmanniae Preparata (Shudihuang) 15 g; (b) Fructus Corni (Shanzhuyu) 12 g; (c) Herba Cistanches (Rousongrong) 15 g; (d) Herba Epimedii 15 g; epimedium herb (Yinyanghuo) the dried above ground parts of *Epimedium brevicornum* Maxim., *Epimedium sagittatum* (Sieb. et Zucc.) Maxim., *Epimedium pubescens* Maxim., *Epimedium wushanensis* T. S. Ying and *Epimedium koreanum* Nakai; (e) Radix Aconiti Lateralis Preparata (Fuzi) 6 g; (f) Radix Ophiopogonis (Maidong) 15 g; (g) Rhizoma Anemarrhenae 15 g; common anemarrhena rhizome (Zhimu), the dried rhizome of *Anemarrhena asphodeloides* Bge.; (h) Rhizoma Acori Tatarinowii (Shichangpu) 6 g; (i) Radix Polygalae (Yuanzhi) 6 g; (j) Fructus Trichosanthis seed 30 g; snakegourd seed (Gualouren), the dried seed of *Trichosanthes kirilowii* Maxim. or *Trichosanthes rosthornii* Harms.; (k) Scorpio 6 g; scorpion (Quanxie), the dried body of artificial breeding of *Buthus martensii* Karsch.; (l) Agkistrodon 9 g; long-nosed pit viper (Qishe), the dried body of artificial breeding of *Agkistrodon acutus* (Guenther). The prescription was prepared from the water decoction and oral for twice daily and the patient has been using it continuously for 12 years.

During the 12 years, DHYZ has been modified according to the mainly accompanied syndrome or symptoms as follows (Table 3): (1) Qi deficiency: plus Radix Astragalus seu Hedysari, milkvetch root (Huangqin), the dried roots of *Astragalus membranaceus* (Fisch.) Bge. var. *Mongolicus* (Bge.) Hsiao or *A membranaceus* (Fisch.) Bge.; and Radix Ginseng, ginseng (Rensheng), the dried roots of *Panax ginseng* C. A. Mey.; (2) obvious yin deficiency: plus Radix Rehmanniae Recens, unprocessed rehmannia root (Shengdihuang), the dried roots of *Rehmannia glutinosa* Libosch.; Fructus Ligustri Lucidi, glossy privet fruit (Nvzhenzi), the dried ripe fruit of *Ligustrum lucidum* Ait.; and Herba Ecliptae, yerbadetajo herb (Hanliancao), the dried stems of *Eclipta prostrata* L.; (3) accumulation of phlegm-fire: minus Radix Aconiti Lateralis Preparata (Fuzi) and Cortex Cinnamomi (Rougui); Plus Concretio Silicea Bambusae, tabasheer (Tianzhuhuang), the saps from *Bambusa textilis* McClure or *Schizostachyum chinense* Rendle, succus bambusae; fresh bamboo sap (Zhuli), the saps from *Bambusa tuldoidea* Munro or *Sinocalamus beecheyanus* (Munro) McClure var. *pubescens* P. F. Li or *Phyllostachys nigra* (Lodd.) Munro var. *henonis* (Mitf.) Stapf ex Rendle; and Rhizoma Arisaematis Cum Bile; bile arisaema (Dannanxing), the dried roots of *Arisaema erubescens* (Wall.) Schott or *Arisaema heterophyllum* Bl. or *Arisaema amurense* Maxim.; (4) deficiency of heart blood: plus Semen Ziziphi Spinosa, spine date seed (Suanzaoren), the dried ripe seeds of *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou; Semen Platycladi, Chinese arborvitae kernel (Baiziren), the dried ripe seeds of *Platycladus orientalis* (L.) Franco; and Caulis Polygoni Multiflori, tuber fleeceflower stem (Yejiateng), the dried stems of *Polygonum multiflorum* Thunb.; (5) constipation: optionally plus Rhizoma Anemarrhenae (Zhimu); Semen Trichosanthis (Guolouren); Radix Polygoni Multiflori, fleeceflower root (Heshouwu), the dried roots of *P multiflorum* Thunb.; Semen Persicae, peach seed (Taoren), the dried seeds of *Amygdalus persica* L. or *Amygdalus davidiana* (Carr.) C. de Vos ex Henry; Fructus Cannabis, hemp seed (Maziren), the dried ripe fruit of *Cannabis sativa* L.; Radix Angelicae sinensis, Chinese angelica

(Danggui), the dried roots of *A sinensis* (Oliv.) Diels; Radix Puerariae, kudzuvine root (Gegeng), the dried roots of *Pueraria lobata* (Willd.) Ohwi or *Pueraria thomsonii* Benth; Semen Pruni, Chinese dwarf cherry seed (Yuliren), the dried ripe seeds of *Cerasus humilis* (Bge.) Sok. or *Cerasus japonica* (Thunb.) Lois. or *Amygdalus pedunculata* Pall.; and Herba Cynomorii, songaria cynomorium herb (Suoyang), the dried stems of *Cynomorium songaricum* Rupr.; (6) obvious muscular twitchings: plus Bombyx Batryticatus, stiff silkworm (Jiangcan), the dried body of *Bombyx mori* Linnaeus.; Periostracum Cicadae, cicada slough (Chantui), the dried shell of *Cryptotympana pustulata* Fabricius; Lumbricus, earthworm (Dilong), the dried body of *Pheretima aspergillum* (E. Perrier) or *Pheretima vulgaris* Chen or *Pheretima guillelmi* (Michaelsen) or *Pheretima pectinifera* Michaelsen; Scolopendra, centipede (Wugong), the dried body of *Scolopendra subspinipes mutilans* L. Koch; (7) cervicomuscular weakness: plus Radix Puerariae (Gegeng); and Colla Corni Cervi, deerhorn glue (Lujiaoqiao), the glue of horn of *Cervus nippon* Temminck or *Cervus elaphus* L.; (8) pain of limbs: plus Radix Paeoniae Alba, white peony root (Baishao), the dried stems of *paeonia lactiflora* pall.; Fructus Chaenomelis, common flowering quince fruit (Mugua), the dried ripe fruit of *Chaenomeles speciosa* (Sweet) Nakai; and Herba Siegesbeckiae, siegesbeckia herb (Xixiancao), the dried stems of *Siegesbeckia orientalis* L. or *Siegesbeckia pubescens* Makino or *Siegesbeckia glabrescens* Makino.

Follow-up and Outcomes

After 12-year treatment and follow-up, no obvious adverse event occurred during the treatment period. In addition, the patient still survived with ALS and does not require permanent continuous ventilator till today (Figure 1). The symptoms of choking on liquids are improved, and the utility of 30 mL water swallow test was improved with grade 2. The symptoms of muscle twitching of limbs were also reduced. However, muscle strength worsened slowly as follows: tongue muscle atrophy and tongue fasciculations, the slurring of speech, difficulty in communication and use of facial expression, difficulty in activity with both hands and in neck-lifting, muscle wasting of limbs, and presenting with claw hand. Strength in the distal and proximal muscle of the upper bilateral limbs was of grade 0/5 and 1/5 to 2/5 respectively, and muscle strength in the lower bilateral limbs was of grade 2/5, graded on the Medical Research Council Muscle Strength Grading System. At last, we will follow-up the patient continuously. On 7 January 2014, the repeated EMG showed motor conduction amplitude reducing gradually and velocity not changing more when compared with the initial EMG (Table 2).

DISCUSSION

This is a long-term follow-up study on a case with ALS treated by TCM prescription. A middle-aged woman was diagnosed with ALS based on the revised El escorial criteria. After consuming orally administrated riluzole 100 mg daily for 10 months, she stopped this drug and then started DHYZ that she has been using for 12 years. The main findings were that DHYZ therapy for ALS may potentially improve bulbar paralysis, delay use of ventilator support, and prolong survival time; there were fewer adverse effects.

ALS is an adult-onset fatal neurodegenerative disorder affecting motor neurons. Approximately 90% of ALS cases are sporadic, but the remaining 10% of the cases are familial.¹ The mean age of onset is 58 to 63 years in sporadic and 43 to 52

TABLE 3. Accompanied with Syndrome or Symptom and Corresponding Modified Dihuang Yinzi for Amyotrophic Lateral Sclerosis

Accompanied with Syndrome or Symptom	Diagnostic Suggestion	Method of Treatment	Modified Dihuang Yinzi
Qi deficiency	Lassitude, general weakness, weakness of the extremities, shortness of breath, low voice, pale face, lack of appetite, spontaneous sweating, pale tongue, and weak pulse.	Benefiting qi	Plus Radix Astragali seu Hedysari (Huangqin) and Radix Ginseng (Rensheng)
Obvious yin deficiency	Emaciated appearance, dry throat and mouth, fidgeting, irritability, dry stool, bone-steaming sensation, night sweating, tidal fever, red cheeks, sore back, red tongue, scanty tongue coat, and deep thready rapid pulse.	Nourishing yin	Plus Radix Rehmanniae Recens (Shengdihuang), Fructus Ligustri Lucidi (Nvzhenzi), and Herba Ecliptae (Hanliancao)
Accumulation of phlegm-fire	Coughing, yellowish thick sputum, fullness in the chest, reddened tongue with yellowish greasy coating, and slippery rapid pulse	Clearing away heat and resolving phlegm	Minus Radix Aconiti Lateralis Preparata (Fuzi) and Cortex Cinnamomi (Rougui); Plus Concretio Silicea Bambusae (Tianzhuhuang), succus bambusae (Zhuli), and Rhizoma Arisaematis Cum Bile (Dannanxing)
Deficiency of heart blood	Insomnia, palpitations, dizziness, blurred vision, pale face, sallow facial expression, pale lips, dry and dull nails, palpitation, dry stool, delayed menstruation with pale scanty menstrual discharge, pale tongue, and thready pulse.	Nourishing heart and tranquilizing mind	Plus Semen Ziziphi Spinosae (Suanzaoren), Semen Platycladi (Baiziren), and Caulis Polygoni Multiflori (Yejiateng)
Constipation		Moistening intestines to relieve constipation	Optionally plus Rhizoma Anemarrhenae (Zhimu), Semen Trichosanthis (Guolouren), Radix Polygoni Multiflori (Heshouwu), Semen Persicae (Taoren), Fructus Cannabis (Maziren), Radix Angelicae Sinensis (Danggui), Radix Puerariae (Gegeng), Semen Pruni (Yuliren), and Herba Cynomorii (Suoyang)
Obvious muscular twitchings		Extinguishing wind and harmonizing collaterals	Plus Bombyx Batryticatus (Jiangcan), Periostracum Cicadae (Chantui), Lumbricus (Dilong), and Scolopendra (Wugong)
Cervicomuscular weakness		Warming yang and tonifying essence, raising Yang and benefiting the neck muscles	Plus Radix Puerariae (Gegeng) and Colla Corni Cervi (Lujiaojiao)
Pain of limbs		Nourishing Yin and relieving pain, strengthening the sinews and unblocking the channels and collaterals	Plus Radix Paeoniae Alba (Baishao), Fructus Chaenomelis (Mugua), and Herba Siegesbeckiae (Xixiancao)

years in familial cases of ALS.¹⁴ Only 5% of the cases of ALS have an onset <30 years of age.¹⁵ An increased risk in the sex incidence ratio was male:female = 1.5:1.² In the present case, a female suffering from ALS was of age 38 years in sporadic who presented with limb onset and subsequently bulbar symptoms.

ALS is primarily a clinically diagnosed disease because of the lack of an established biological marker. Diagnosis of ALS

is usually straightforward according to the progressive, generalized symptoms in the limb and bulbar regions.¹⁶ This can result in a delay in diagnosis because ALS inclines to be focal in onset presented with few clinical signs in the early disease course. The mean lag time between the onset of symptoms of ALS and confirmation of the diagnosis is 10 to 18 months.¹⁷ In 1994, the El Escorial criteria for diagnosing ALS clinically were



FIGURE 1. A case of amyotrophic lateral sclerosis patient was treated by using a classical Chinese herbal prescription Dihuang Yinzi, who has survived 12 years with significant improvement in bulbar paralysis and don't require permanent continuous ventilator till now. (A) The patient's appearance; (B) The patient's tongue muscle atrophy; (C) The patient's feet; (D) The patient's palms.

published by a subcommittee on ALS of the world federation of neurology and the revisited criteria were revised in 1999, which included the clinical neurophysiological measurements as diagnostic tools to exclude differential diagnosis.¹² In 2006, the Awaji criteria¹⁸ placed equal emphasis on both electromyographic evidence of degeneration and clinical abnormalities, thereby potentially enabling an earlier secure diagnosis of ALS, and this criterion has successfully increased in sensitivity to detect patients with ALS but additionally showed that this is achieved without increasing the number of false-positives.¹⁹ In 2015, an updated version of El Escorial criteria for the diagnosis of ALS was published with the purpose of both clinical practice and clinical trial.²⁰ The new diagnostic criteria of ALS require at least one of the following: (1) progressive upper and lower motor neuron deficits in at least one limb or region of the human body; that is, that is meeting the revised El Escorial criteria for possible ALS; (2) lower motor neuron deficits as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, and lumbosacral). The EMG findings consist of neurogenic potentials and

fibrillation potentials and/or sharp waves. In the present study, the patient was diagnosed with ALS according to revised El Escorial criteria 2000 and confirmed both clinical and electrophysiological evidences during long-term follow-up. Electrophysiological evaluation is important for the diagnosis of ALS. As for this patient, repeated investigations were required and the diagnosis can be confirmed with disease progression over time. In the initial EMG, the damages of different extents occurred in motor nerves which were controlled by neurogenic changed muscle of the patient. The patient's sensory nerve conduction was normal. Motor conduction velocity in the upper and lower limbs was almost normal despite the amplitude decreased in the initial and repeated examination, because the primary abnormality of the peripheral nerve was axonal loss, rather than demyelination. It is critical that tongue innervated by a cranial nerve demonstrated evidence of acute reinnervation confirmed the diagnosis for the positive changes of resting potential, for example, fibs and wave. From the repeated EMG, we can find motor conduction amplitude reducing gradually and velocity not changing more when compared with the initial EMG.

Despite advances in the treatments and interventions, there are no medications that stop or reverse the progressive loss of motor neurons of ALS because of uncertainty on the pathogenic mechanisms underlying degeneration of motor neuron. Riluzole remains the only available neuroprotective/disease-modifying drug for ALS, with only marginal effects on disease survival.⁵ Although still incurable, ALS is not untreatable. Over the past two decades, remarkable progression in integrative and aggressive supportive care has altered the quality of life of ALS patient. In addition, emphasis has been made in therapies that may even improve the disease course of ALS. Presently, ALS is considered as a complex disease with broad pathophysiological framework and numerous theories, including oxidative stress, glutamate and neuronal cytotoxicity, protein aggregation, mitochondrial impairment, cytoskeletal disruption, inflammation, apoptotic cell death, and altered regulation of gene expression.²¹ Thus, combined therapies that focus on more than one pathogenic pathway may slow disease progression in multiple targets/organs interactions. Impressively, the key to TCM prescription is to choose a combination of CHMs guided the combinatorial principle of Sovereign-Minister-Assistant-Envoy according to the patient's syndrome in order to regain the balance state of body functions.²² Over the past decades, many experimental and clinical studies demonstrated TCM prescriptions; herbal components may have multiple targets and exert neuroprotection or treatment of ALS.^{8,23} Pharmacological studies indicated that DHYZ exerts neuroprotective function. For example, DHYZ possesses neuroprotective and antidementia properties through preventing the loss of neural cells and synapses in rats of ischemic brain injury.²⁴ Many studies have demonstrated that each ingredient or its active components of DHYZ exerted potential neuroprotective functions (Table 1). Rehmannia root and Catalpol have antioxidation, antiapoptosis, antiinflammation, and other neuroprotective properties and act in neuroprotection of neurodegenerative diseases.^{25,26} *p*-coumaric acid, ursolic acid, and gallic acid from Corni fructus exerted antioxidation, antiapoptosis, and antineuroinflammation against A β -induced toxicity.^{27,28} Herba Cistanches and its active components possess neuroprotective function, hormone regulation, immunomodulatory, antioxidative, antiapoptotic, and antiinflammatory activities, making them potential treatment for various neurodegenerative disorders.²⁹ β -D-fructofuranosyl (2–2) β -D-fructofuranosyl from Radix Morindae Officinalis enhanced antioxidative activity, antiapoptotic activity, and energy metabolism against A β -induced neurotoxicity.³⁰ Fuzi polysaccharide-1 affected brain-derived neurotrophic factor-signaling pathways in the hippocampus.³¹ Cortex Cinnamomi has a neuroprotective effect on glutamate-induced neuronal death through the inhibition of Ca²⁺ influx;³² 2'-hydroxycinnamaldehyde has antineuroinflammatory and neuroprotective effects in the central nervous system by targeting lipoprotein receptor-related protein 1.³³ An active compound from Dendrobium and Chrysotoxine exhibit antioxidant, antiapoptosis, and neuroprotective activities against neurotoxin-induced cell death.^{34,35} *O japonicus* displays antiinflammatory, antioxidative, and immunomodulative activities.³⁶ Schisantherin A, schisandrin B, and schisandrin C from Fructus Schisandrae Chinensis attenuate abnormal oxidative stress and modulate the apoptotic signal pathway, exhibiting their neuroprotective function on neurodegenerative diseases.^{37,38} β -asarone and eugenol, components of Rhizoma Acori Tatarinowii, have neuroprotective function cells through inhibiting apoptosis against A β -induced neurotoxicity.³⁹ Polygalae radix has neuroprotective effects against toxin-induced

neuronal death through its antioxidant and antiapoptotic activities;⁴⁰ its ethanol extracts as a novel autophagy inducer modulate neurodegenerative disorders via reducing toxicity and clearing of mutant proteins in the cellular level.⁴¹ *P cocos* water extract has neuroprotective action against A β -induced neuronal injury through suppressing the oxidative stress and the apoptosis.⁴²

In conclusion, we reinforce that TCM prescription, especially DHYZ, can be potentially used in ALS patients because of its multitargeted neuroprotection and general safety, although ALS has not a cure. In addition, we identified the area that is worthy of further study and DHYZ as a promising candidate for further clinical application and ALS trials. Further rigorous randomized controlled trials are needed.

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