Editorial

# Amyotrophic Lateral Sclerosis: Precise Diagnosis and Individualized Treatment

**Qing-Qing Tao, Zhi-Ying Wu**

Department of Neurology and Research Center of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China

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## Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by selective death of upper motor neurons (UMNs) and lower motor neurons (LMNs), typically may die from respiratory failure within 2–5 years of symptom onset.[1] About 10% of ALS patients are familial whereas the remaining patients are sporadic. ALS is highly heterogeneous in genetic and clinical phenotype, with lack of definitive diagnostic tools, making it extremely difficult to make early diagnosis. Considerable resources have been devoted to unravel the pathogenesis of ALS since the first pathogenic gene *SOD1* was found in 1993. With the advances in sequencing and genome technology, the pace of pathogenic gene discovery has been greatly accelerated. At present, more than 20 ALS genes including *SOD1, TARDBP, FUS, C9ORF72, OPTN, VCP, UBQLN2, PFN1, TBK1*, and *CHCHD10* have been discovered.[2,3] Several potential molecular pathways leading to motor neuron degeneration have been identified.[4] Although riluzole and edaravone (RADICAVA) have been shown to slow the disease progression and have a modest improvement in survival by several months,[5] currently, ALS is still lack of effective cures. Here, we discuss the problems in precise diagnosis and individualized treatment of ALS patients.

## Precise Diagnosis of Amyotrophic Lateral Sclerosis

### Problems in diagnosis of amyotrophic lateral sclerosis

According to the El Escorial criteria and its revisions, diagnosis of ALS relies on identification of UMN and LMN signs within different body regions defined as bulbar, cervical, thoracic, and lumbar, respectively. In the early stage of ALS, misdiagnosis remains a common clinical problem, particularly for young clinicians who did not receive specific training on neuromuscular disorders. Diagnosis can be difficult at early stage partly because ALS showed great clinical variability in presentation and prognosis. The patients can be demonstrated as limb onset or bulbar onset, and neurological signs can be UMN or LMN lesion only or both. And, in limb-onset cases, symptoms may appear distally or proximally in either the upper or lower limbs. Besides, a broad spectrum of disorders called as ALS mimic syndromes should be taken into account in the differential diagnosis. So far, no specific biomarkers or tests are available to distinguish them although a number of studies have reported several potential biomarkers.[6-8] For instance, the plasma galectin-3 level has been reported to be significantly increased in ALS patients with limb-onset in Chinese population.[9]

As ALS is a disabling and life-threatening disease, misdiagnosis will give substantial implications for patients and caregivers.[10] Many clinicians tend not to make an ALS diagnosis which leading to diagnostic delay. The mean time from the onset of symptoms to confirmation of the diagnosis is 10–18 months according to EFNS guidelines.[11] Recent years, with the progress of our knowledge in pathogenesis of ALS and the insights from clinical drug test performed in several neurodegenerative diseases, more and more clinicians

**Address for correspondence:** Prof. Zhi-Ying Wu, Department of Neurology and Research Center of Neurology, Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Rd., Hangzhou, Zhejiang 310009, China
E-Mail: zhiyingwu@zju.edu.cn

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recognized the importance of early diagnosis of ALS. An early and accurate diagnosis is not only essential for ALS patients to receive specific clinical management but also important for the correct inclusion of patients in clinical trials.

### Diagnosing amyotrophic lateral sclerosis early and accurately

First of all, carefully record the patient's chief complaint and the history of symptom development, followed by the family history, personal history, and any clinical features regarding the main body systems according to standard practice. A systemic neurological examination is crucial to achieve an accurate diagnosis.

Second, diagnosis should base on standardized criteria. The El Escorial criteria which developed by the World Federation of Neurology Research Group on Motor Neuron Diseases were the most accepted diagnostic criteria for ALS, though these criteria were originally developed for research purposes. The levels of diagnosis depended on clinical assessment of the extent and distribution of UMN and LMN lesion. These criteria were specific for ALS;[12] however, sensitivity is a challenge, especially in the early stages of the disease, leading to diagnostic delay and limiting the accurate diagnosis of ALS. The El Escorial criteria underwent several revisions. The Awaji-Shima criteria (revision in 2008) recommend using electrophysiological data in the diagnosis of ALS. The Chinese Medical Association criteria (2012) were developed on the Awaji-Shima criteria [Table 1]. Several studies reported that these criteria have higher diagnostic sensitivity, supporting that electromyography (EMG) should be performed in early stage.[13] Some developing LMN degeneration is detectable only on EMG which is in line with a series of studies focused on the usage of EMG in ALS early diagnosis and the disease progression assessment.[6,7] Subclinical UMN dysfunction may be identified by transcranial magnetic stimulation techniques. Besides, tests to rule out other ALS mimic syndromes may include routine laboratory tests, EMG, nerve conduction study, magnetic resonance imaging (MRI), lumbar puncture, and sometimes muscle biopsy.

For familial ALS (FALS) cases, the targeted sequencing approach which was designed covering all of the already known mutations should be performed to identify the pathogenic mutations.[3,14] However, nearly more than 30% of the FALS cases still have unidentified genetic etiology. For these cases, additional genetic tests such as whole exon sequencing or whole genome sequencing were needed to unravel the disease-causing mutations.[15]

Another important and useful strategy to help early diagnosis is to establish a patients' database and follow-up system. A patents' database should carefully record all aspects of patients' features including age, family history, site of onset, symmetry, severity of symptoms, balance of UMN and LMN involvement, extramotor features, disease progression, prognosis, and all tests data. As ALS is a progressively developed disease, patients in early stage may have symptoms limited to one or two regions that are difficult to identify and make a diagnosis. A follow-up system will help to early recognize the disease during its progression. Patients with an ALS suspicion should be evaluated at least in 3–6 months in specialized ALS center. Besides, it is necessary to well communicate with patients, so that patients will understand and cooperate with the doctor's diagnosis and treatment plan.

Finally, the most important point which deserves additional attention is when the diagnosis is unclear, it is recommended to refer patients to the ALS specialists, which can greatly minimize the diagnostic delay.

## Individualized Treatment of Amyotrophic Lateral Sclerosis

### Clinical management of amyotrophic lateral sclerosis patients

Although mean survival in ALS patients is only 2–5 years, some of the patients tend to have a more slowly progressive

**Table 1: Criteria of amyotrophic lateral sclerosis**

| Criteria | Clinically definite ALS | Clinically probable ALS | Clinically possible ALS | Suspected ALS |
|---|---|---|---|---|
| El Escorial criteria (1994) | UMN and LMN signs in three regions of the body | UMN and LMN signs in at least two regions, with some UMN sign rostral to LMN signs | UMN and LMN signs in only one region, or UMN signs alone in two or more regions, or LMN signs rostral to UMN signs | LMN signs only |
| Awaji-Shima criteria (2008) | Clinical or electrophysiological evidence of UMN and LMN signs in the bulbar region and at least two spinal regions, or UMN and LMN signs in three spinal regions | Clinical or electrophysiological evidence of UMN and LMN signs in at least two regions, with some UMN signs rostral to LMN signs | Clinical or electrophysiological evidence of UMN and LMN signs alone in two or more regions, or LMN signs rostral to UMN signs | |
| Chinese Medical Association criteria (2012) | Clinical or electrophysiological evidence of UMN and LMN signs in at least at three regions | Clinical or electrophysiological evidence of UMN and LMN signs in at least two regions, with some UMN signs rostral to LMN signs | Clinical or electrophysiological evidence of UMN and LMN signs in one region, or UMN signs alone in two or more regions | |

ALS: Amyotrophic lateral sclerosis; UMN: Upper motor neuron; LMN: Lower motor neuron.

disease form and can survive for over a decade, demonstrating the importance of clinical management throughout the course of the disease. So far, there is no breakthrough for the treatment of ALS. The main treatments are neuroprotective treatment, symptomatic and supportive treatment as well as some unproven disease-modifying therapies such as stem cell transplantation and gene therapy. Multidisciplinary specialist team can provide optimized individualized clinical management for patients with ALS. The Revised ALS Functional Rating Scale is the most accepted and widely used assessment tool during the course of the disease.

### Unapproved disease-modifying therapies

Stem cell transplantation therapy is still practiced in animal model level or under clinical trial. A new stem cell treatment that injected intramuscularly and intrathecal administration of autologous mesenchymal stem cells in patients with ALS was successful in slowing disease progression in a small group of ALS patients in a Phase 2 clinical trial,[13] showing this therapy may have possible clinical benefit.

Gene therapy is a molecular level intervention for the treatment of the disease. It has greatly broadened the prospects of disease's treatment. However, this therapy is only developed for familial patients who carry specific gene mutations and is not suitable for most sporadic patients who have no specific target. It still needs a long way to enter the clinical stage of treatment.

### Neuroprotective treatment

Medication with riluzole should be initiated as early as possible. Another neuroprotective drug edaravone (RADICAVA) has also been approved by the Food and Drug Administration recently. However, both of them have a modest improvement in survival by several months. Clinicians should pay more attention on individualized treatment for ALS patients, improving the overall life quality of patients. A recent study pointed out that formal classification systems such as the El Escorial criteria and the International Classification of Diseases are lack of features that are important for clinical management, for example, site of onset, extramotor features, rate of progression, genetic basis, and functional effect.[16] All of these individualized clinical features should carefully record in the patient's database which may give guidance information during the course of the disease.

### Symptomatic treatment and supportive care

Evidence-based symptomatic treatment of complications is important to improve patients' life quality.[11] Depression and anxiety frequently occur in patients and their caregivers, particularly prevalent during the diagnostic and terminal phases. Empirically tricyclic antidepressants and selective serotonin reuptake inhibitors are effective. For most patients, sialorrhea is common and sometimes socially disabling. Symptomatic treatment drugs such as amitriptyline oral doses of 5–10 mg three times a day are often sufficient. Cramp is also a troublesome symptom. Levetiracetam is shown to be beneficial. Physical therapy is the mainstay of effective treatment of spasticity in ALS patients. Medullary paralysis is another suffering symptom for patients, particular for the bulbar onset patients who have this symptom in an early stage. Percutaneous endoscopic gastrostomy feeding will greatly improve nutrition and quality of life. Ventilator involvement may occur in terminal phases. Noninvasive positive-pressure ventilation improves survival and quality of life.

Dietary counseling is a common concern for patients. Education of patients and their caregivers in feeding high-protein and high-caloric foods is important as weight loss is an independent prognostic factor of survival in ALS. Another concern that patients want to know is the course of the disease. In this case, the biomarkers that could reflect the disease progression are useful for management. Slower elimination rate of serum lactate has been reported to be associated with faster disease progression in Chinese patients.[17] The introduction of alternative communication devices is needed for maintaining the patients' ability to communicate which is usually affected by dysarthria. As the evidence base for symptomatic treatment increases, individual decisions become more complex. With the rich amount of information on unproven therapies available on the internet, patients' choices are further complicated that they often make decisions about their medical care using these sources. Thus, patients and caregivers must be fully and reliably informed about their options.

## Conclusions and Future Prospects

We have come a long way since the first ALS pathogenic gene *SOD1* was discovered 20 years ago. However, great challenges still exist in all aspects of the disease including diagnosis, pathogenesis, and treatment that far from be fully addressed. Further work is needed to strengthen the cooperation between ALS experts' teams. We need to build a standard ALS diagnostic and treatment criteria that can provide enriched, broaden spectrum of phenotypic information about ALS based on Chinese patients. Establish patients' database that linking signs, symptoms, laboratory findings, results from imaging studies, and follow-up information together will help develop diagnostic and prognostic biomarkers. A nationwide shared resource platform will be helpful for integrating multicenter clinical data and human sample resource which can accelerate the research on ALS pathogenesis as well as the step to find new therapeutic drugs. Discovery of effective disease-modifying therapies remains a critical need for patients with this devastating disease.

## References


1. Hardiman O, van den Berg LH, Kiernan MC. Clinical diagnosis and management of amyotrophic lateral sclerosis. Nat Rev Neurol 2011;7:639-49. doi: 10.1038/nrneurol.2011.153.
2. Al-Chalabi A, van den Berg LH, Veldink J. Gene discovery in amyotrophic lateral sclerosis: Implications for clinical management. Nat Rev Neurol 2017;13:96-104. doi: 10.1038/nrneurol.2016.182.

3. Liu ZJ, Li HF, Tan GH, Tao QQ, Ni W, Cheng XW, *et al.* Identify mutation in amyotrophic lateral sclerosis cases using HaloPlex target enrichment system. Neurobiol Aging 2014;35:2881.e11-5. doi: 10.1016/j.neurobiolaging.2014.07.003.
4. Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci 2013;14:248-64. doi: 10.1038/nrn3430.
5. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev 2012:CD001447. doi: 10.1002/14651858.CD001447.pub3.
6. Liu MS, Niu JW, Li Y, Guan YZ, Cui LY. Quantitating changes in jitter and spike number using concentric needle electrodes in amyotrophic lateral sclerosis patients. Chin Med J 2016;129:1036-40. doi: 10.4103/0366-6999.180533.
7. Fang J, Cui LY, Liu MS, Guan YZ, Li XG, Cui B, *et al.* F Wave study in amyotrophic lateral sclerosis: Assessment of segmental motoneuronal dysfunction. Chin Med J 2015;128:1738-42. doi: 10.4103/0366-6999.159346.
8. Fang J, Liu MS, Guan YZ, Cui B, Cui LY. Importance of sample size for the estimation of repeater F waves in amyotrophic lateral sclerosis. Chin Med J 2015;128:515-9. doi: 10.4103/0366-6999.151107.
9. Yan J, Xu Y, Zhang L, Zhao H, Jin L, Liu WG, *et al.* Increased expressions of plasma galectin-3 in patients with amyotrophic lateral sclerosis. Chin Med J 2016;129:2797-803. doi: 10.4103/0366-6999.194656.
10. Cui B, Cui LY, Liu MS, Li XG, Ma JF, Fang J, *et al.* Behavioral symptoms in motor neuron disease and their negative impact on caregiver burden. Chin Med J 2015;128:2295-300. doi: 10.4103/0366-6999.163393.
11. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, *et al.* EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – Revised report of an EFNS task force. Eur J Neurol 2012;19:360-75. doi: 10.1111/j.1468-1331.2011.03501.x.
12. Schrooten M, Smetcoren C, Robberecht W, Van Damme P. Benefit of the Awaji diagnostic algorithm for amyotrophic lateral sclerosis: A prospective study. Ann Neurol 2011;70:79-83. doi: 10.1002/ana.22380.
13. Petrou P, Gothelf Y, Argov Z, Gotkine M, Levy YS, Kassis I, *et al.* Safety and clinical effects of mesenchymal stem cells secreting neurotrophic factor transplantation in patients with amyotrophic lateral sclerosis: Results of phase 1/2 and 2a clinical trials. JAMA Neurol 2016;73:337-44. doi: 10.1001/jamaneurol.2015.4321.
14. Liu ZJ, Lin HX, Liu GL, Tao QQ, Ni W, Xiao BG, *et al.* The investigation of genetic and clinical features in Chinese patients with juvenile amyotrophic lateral sclerosis. Clin Genet 2017. [Epub ahead of print]. doi: 10.1111/cge.13015.
15. Liu Q, Shu S, Wang RR, Liu F, Cui B, Guo XN, *et al.* Whole-exome sequencing identifies a missense mutation in hnRNPA1 in a family with flail arm ALS. Neurology 2016;87:1763-9. doi: 10.1212/WNL.0000000000003256.
16. Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LH. Amyotrophic lateral sclerosis: Moving towards a new classification system. Lancet Neurol 2016;15:1182-94. doi: 10.1016/S1474-4422(16)30199-5.
17. Zhang YJ, Fan DS. Elimination rate of serum lactate is correlated with amyotrophic lateral sclerosis progression. Chin Med J 2016;129:28-32. doi: 10.4103/0366-6999.1725.