

Considerations on the concept, definition, and diagnosis of amyotrophic lateral sclerosis

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Abstract

The concept, definition, and diagnosis of amyotrophic lateral sclerosis (ALS) currently present some problems. This article systematically reviews the literature on the history, current concepts, definition, and diagnosis of ALS, and discloses the present problems based on the retrieved literature and the authors' clinical experience. The current concepts and definitions of ALS have not yet been unified or standardized in clinical practice, and are sometimes vague or inaccurate, which can cause difficulties for neurologists in the clinical treatment of ALS. The concept and definition of ALS need to be further ascertained, and the current diagnostic criteria for ALS require further development. The identification of effective and objective biomarkers may be a feasible method for the early and accurate diagnosis of ALS. Therefore, future research should focus on the identification of reliable biomarkers—especially neuroimaging biomarkers—through autopsy. Standardizing the concept and definition of ALS and formulating clear diagnostic criteria will largely avoid many uncertainties in the future clinical research and treatment of ALS, which will greatly benefit patients.

Key Words: amyotrophic lateral sclerosis; clinical symptoms; concept; definition; diagnosis; familial amyotrophic lateral sclerosis; motor neuron disease; muscle atrophy

Introduction

Amyotrophic lateral sclerosis (ALS) is a specific disease initiated by the death of neurons controlling voluntary muscles. The main clinical manifestations of ALS are progressive stiffness, convulsions, and worsening muscle weakness caused by chronic muscle atrophy; this results in difficulty in speech, dysphagia, and eventually dyspnea (Zarei et al., 2015; Brown and Al-Chalabi, 2017). This disorder leads to muscle weakness and atrophy throughout the body, which is caused by the degeneration of both upper motor neurons (UMNs) and lower motor neurons (LMNs) (Riancho et al., 2019; Gonzalez-Fernandez et al., 2020). Individuals affected by the disease may ultimately lose the ability to initiate and control all voluntary movement, although bladder and bowel function and the muscles responsible for eye movement are usually spared until the final stages of the disease (Sun et al., 2012; Hobson and McDermott, 2016; Niedermeyer et al., 2019). Some ALS patients also present mild cognitive or behavioral dysfunction in the middle and/or late stages (Hobson and McDermott, 2016; Martin et al., 2017). Examples of behavioral dysfunction include repeating phrases or gestures, apathy, and a loss of inhibition (Raaphorst et al., 2012). Cognitive dysfunction can include language dysfunction, executive dysfunction, and troubles with social cognition and verbal memory (Beeldman et al., 2016). Sensory nerves and the autonomic nervous system are generally unaffected, and most ALS patients maintain the senses of hearing, sight, touch,

smell, and taste.

At present, there are no treatments that can cure or prevent the progression of ALS. Studies have shown that riluzole might extend patients' lifespans by 2–3 months (Cai and Yang, 2019). In addition, the US Food and Drug Administration recently approved a reactive oxygen species scavenger, edaravone, to be used in the treatment of ALS; however, its curative effects need further clinical verification in larger trials of ALS patients and control individuals (Jaiswal, 2019). Furthermore, non-invasive ventilation can also improve the quality of life and lifespan of ALS patients (Dorst and Ludolph, 2019).

ALS can affect people of any age, but usually occurs around the age of 60 years (Kiernan et al., 2011). The survival time from morbidity to death in most ALS patients is usually 3–5 years (Hobson and McDermott, 2016). Approximately 10% of ALS patients survive for longer than 10 years after clinical onset (Kiernan et al., 2011), and the survival time of a few ALS patients, like guitarist Jason Becker and cosmologist Stephen Hawking, has exceeded 30 years. However, most ALS patients die of respiratory failure within 5 years after clinical onset (Kiernan et al., 2011; Chazot-Balcon et al., 2019). In many countries, including China, the current incidence of ALS remains unclear (Kiernan et al., 2011). In the European and American populations, the incidence rates of ALS are around two people per 100,000 per year (Traynor et al., 1999, 2001; Mandrioli et al., 2003; Logroscino et al., 2005; Kiernan et al., 2011).

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Review

The etiology of 90–95% of ALS remains unknown. Five to ten percent of ALS patients have inherited familial forms of the disease (Kiernan et al., 2011; Yamashita and Ando, 2015). Thus, the current diagnosis of ALS depends mainly on clinical symptoms and signs observed through clinical visits and various examinations. Other potential causes of such symptoms are then excluded using current medical testing technology (McDermott and Shaw, 2008).

ALS is sometimes called motor neuron disease (MND; Davenport et al., 1996; McDermott and Shaw, 2008), which is classified into subtypes in most countries (Ludolph et al., 2012; Zarei et al., 2015). The concepts and definitions of ALS and MND are mixed, and are used in many research studies and clinical work (Davenport et al., 1996; McDermott and Shaw, 2008; Ludolph et al., 2012; Zarei et al., 2015). The concept and definition of ALS have not yet been unified or standardized in clinical practice, and are sometimes vague or inaccurate. We believe that problems remain regarding the concept, definition, and diagnosis of ALS. In this review, we therefore describe the history of ALS as well as the current concepts, definition, and diagnosis of the disease, and then discuss any existing doubts.

Search Strategy

For the present review, we searched the literature using keywords, including amyotrophic lateral sclerosis, muscle atrophy, motor neuron disease, familial ALS, concept, definition, clinical symptoms, diagnosis, and question. We searched for these keywords on PubMed, Google Scholar, WanFang, and in various medical guidelines from the beginning to May 2020. In addition, we used modifications of the main keywords to thoroughly search and systematically review the literature on the history, current concepts, definition, and diagnosis of ALS. We also analyzed the current problems related to these features, based on the retrieved literature as well as difficulties that we have encountered in our clinical work. The literature review was performed with strict control of the data to assemble the foundations of these problems. The problems and proposals extracted from our literature review and clinical experiences are presented herein.

Problems Related to the Concept or Definition of Amyotrophic Lateral Sclerosis

ALS is usually known as MND in the United Kingdom (McDermott and Shaw, 2008). However, MND is currently used to refer to a group of diseases, including ALS. ALS became well known in the United States in the 20th century, when the famous American baseball player Lou Gehrig was diagnosed with the disease in 1939. Thus, ALS is also commonly known as Lou Gehrig's disease in the United States. Later, this disease became well known worldwide when the famous English cosmologist Stephen Hawking was diagnosed with ALS in 1963. ALS also became a well-known disease in 2014 after the "ice bucket challenge" inspired a fundraising activity for ALS research (Song, 2014).

The word "amyotrophic" comes from the Greek "amyotrophia," where "a-" means "no," "myo" refers to "muscle," and "trophia" means "nourishment." "Amyotrophic" therefore means "non-nutritive muscle," which describes the characteristic atrophy of involved muscles that occurs in this disease. "Lateral" refers particularly to the area known as the lateral funiculus, located in the brain and spinal cord, which includes the corticobulbar and corticospinal tracts. The latter consists of the lateral and anterior corticospinal tracts. Degeneration in these areas leads to scarring or hardening, which is known as "lateral sclerosis." Thus, based on the original concept and definition of ALS, this disease must only have the symptoms and signs of muscle atrophy and lateral funiculus sclerosis (Chazot-Balcon et al., 2019).

In commonwealth countries, the term "MND" is commonly used instead of ALS. MND is considered to be a concept and definition that is equal to ALS in clinical and basic research (McDermott and Shaw, 2008). However, the other European countries (excluding the commonwealth) usually use the concept and definition of ALS, and consider that ALS is a subtype of MND. In the United States and China, people also use the concept and definition of ALS for clinical and basic research, and classify MND into four subtypes, including ALS (Fan et al., 2009). Thus, generally speaking, the concepts and definitions of ALS and MND are not unified worldwide. This is likely because the current concepts and definitions of both ALS and MND are somewhat deficient in accurately describing the disease.

The concept and definition of ALS is based on its pathological name, which states that ALS is a disease combining muscle atrophy and sclerosis of the lateral funiculus. Therefore, the preliminary concept and definition of ALS is that it is a disease that damages motor neurons of the brain, brainstem, and spinal cord at the same time. However, with the progression of ALS research, it has become apparent that ALS is a rapidly progressive and fatal disease that not only affects motor neurons in the cerebrum, brainstem, and spinal cord that control voluntary muscle movement, but also damages some neurons associated with cognitive or behavioral functions (Hobson and McDermott, 2016; Martin et al., 2017; Cai and Yang, 2019). In light of these findings, it seems that the original concept and definition of ALS is inappropriate for both research and clinical work. In addition, problems remain with regard to the concept and definition of ALS. For example, some countries consider that ALS and MND are equal in concept and definition, whereas other countries think that ALS is a subtype of MND, and that MND is a group of diseases that includes four subtypes (ALS, primary lateral sclerosis [PLS], progressive muscular atrophy [PMA], and progressive bulbar palsy [PBP]) (Raman et al., 2015).

Both ALS and PLS are pathological concepts and definitions, and are thus more accurate than other concepts and definitions; however, this also means that autopsy evidence is generally required for diagnosis (Chazot-Balcon et al., 2019). There is no useful technique for detecting the pathological changes of lateral sclerosis in surviving ALS patients, and it is not enough to judge sclerosis lesions of the lateral cord by clinical signs—such as pathological signs and tendon hyperreflexia—alone. In contrast, PMA and PBP are defined according to clinical symptoms and signs, but neurologists cannot completely rule out any undiscovered and potentially pathological changes of lateral sclerosis using existing clinical diagnostic techniques, and thus cannot completely rule out the possibility of subsequent ALS development. As well as the aforementioned problems, MND is defined as a disease or a group of diseases that only damages motor neurons, while ALS is not a disease that only damages motor neurons (Hobson and McDermott, 2016; Martin et al., 2017).

It is therefore somewhat incorrect to classify ALS as an MND subtype. We also believe that there are other problems with the classification of MND subtypes. For example, we have found that some patients who are diagnosed early with PLS or PBP can ultimately develop into ALS in the middle or later stages of the disease, suggesting that different MND subtypes may be different manifestations of ALS, rather than independent diseases, at least in most patients (Fan et al., 2009; Ma and Li, 2019). Based on these problems, we believe that the concept and definition of ALS should be updated and reconsidered. We propose that the current concepts and definitions of ALS and MND are not accurate, and that it is not scientifically valid to include ALS as a subtype of MND. We also suggest that Bell-Charcot's disease is a better name for ALS, so that it is named after the scientists who first described the disease, in accordance with international convention—similar

to Parkinson's disease and Alzheimer's disease, for example.

Problems with the Diagnosis of Amyotrophic Lateral Sclerosis

The first ALS diagnostic criteria, proposed by the World Federation of Neurology (WFN) in El Escorial, Spain, in 1994, were developed to use as the standard for diagnosing ALS in clinical work (Brooks, 1994). Using these criteria, a diagnosis of ALS is defined by evidence of LMN impairment, with symptoms and signs obtained through clinical examination and electrophysiological or neuropathological tests. This is accompanied by clinically demonstrated impairment of UMNs, and is followed by the chronic and progressive development of these symptoms and signs (Chazot-Balcon et al., 2019). Nevertheless, it remains necessary to eliminate other diseases that might explain the degeneration of motor neurons, using their electrophysiological, neuroimaging, and pathological characteristics.

However, most investigators who are involved in ALS research have reached the consensus that the aforementioned clinical appearances and electrophysiological findings leave space for doubt when making a diagnosis in some specific situations. For example, most neurologists and specialists in neuromuscular diseases claim that it is very difficult to make an early accurate diagnosis of ALS. The El Escorial diagnostic criteria were therefore revised at the WFN-ALS meeting in Virginia, USA, in 1998. The revised version, known as El Escorial Revisited, was published online by WFN-ALS, with an aim of refining the diagnosis of ALS (Brooks et al., 2000). In this new version, some new methods, including electrophysiology, neuroimaging, immunohistochemistry, and genome analysis, were added to enhance the diagnostic accuracy. The El Escorial Revisited has been regarded as an important step toward alleviating some of the difficulties in ALS diagnosis (Johnsen et al., 2019).

The Awaji criteria was put forward in a meeting about ALS in Japan, with the aim of further improving the diagnostic criteria of ALS (Li et al., 2017). There was a reformulation of the electromyography (EMG) criteria, where fasciculation with signals of neuronal damage was added. Additionally, some new diagnostic methods, including transcranial magnetic stimulation, magnetic resonance imaging (MRI) voxel-based morphometry, and diffuse tensor imaging were also adopted in the revised Awaji criteria. The Awaji criteria recommend that fasciculation should be perceived as equivalent to fibrillation potentials in individuals who are clinically suspected to have ALS (de Carvalho et al., 2008). However, de Carvalho et al. (2011) raised a question in regard to this recommendation: do the Awaji criteria for the diagnosis of ALS put the cart before the horse?

The El Escorial criteria, revised in 2015, are the newest diagnostic criteria for ALS. They propose that a diagnosis of ALS requires at least one of the following: (1) progressive UMN and LMN deficits in at least one limb or region of the body, (i.e., meeting the El Escorial Revisited (Brooks et al., 2000) for possible ALS); and (2) LMN deficits as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, lumbosacral). The EMG findings consist of neurogenic potentials and fibrillation potentials and/or sharp waves. The currently recognized restricted phenotypes of ALS include: (1) PBP; (2) flail arm (Vulpian–Bernhardt) syndrome (FAS) and flail leg syndrome (FLS); (3) PMA; and (4) PLS (Agosta et al., 2015; Ludolph et al., 2015). If PBP extends to both UMN and LMN deficits, or if FAS, FLS, or PMA involve at least two body regions, or if PLS presents with clinical or electrophysiological evidence of LMN involvement in at least one limb or body region, then they can be diagnosed as ALS (Ludolph et al., 2015).

The 1994 El Escorial diagnostic criteria have been recognized as the most useful diagnostic criteria for selecting patients for research trials (Johnsen et al., 2019). However, general neurologists and neuromuscular clinicians often find these criteria unwieldy and generally unhelpful for achieving an early diagnosis of ALS. The El Escorial Revisited was a step toward improving the ALS diagnostic criteria and the diagnostic rate of ALS patients, and allows clinicians more latitude for beginning ALS treatment (Brooks et al., 2000). However, even with the Revised El Escorial diagnostic criteria, the accurate diagnosis of ALS remains a difficult problem that continues to challenge neuromuscular specialists. Earlier diagnosis of ALS based on its progressive and late-appearing clinical manifestations will require more substantial advances in the fields of electrodiagnosis, neuroimaging, immunobiochemistry, and neurogenetics (Belsh, 2000).

When the El Escorial Revisited had been in use for almost 10 years, the Awaji criteria for the diagnosis of ALS were proposed, in 2008. New criteria were added, with some new auxiliary tests, and the importance of neurophysiological data was emphasized; however, these data should be used in the context of clinical information, rather than as a separate, independent set of data. In addition, fasciculation potentials associated with signs of reinnervation are considered evidence of LMN lesions, in particular in cranial-innervated or strong limb muscles. However, fasciculation can also be present in muscles with no motor neuron lesions or death (Bashford et al., 2020). If fasciculation is found in normal muscle, we should therefore be vigilant, because it may be a sign of normal physiological nerve overexcitation or “benign” cramp fasciculation syndrome; it is thus uncertain whether fasciculation indicates a certain LMN lesion (Hart et al., 2002). Therefore, we believe that using the Awaji criteria can lead to the false-positive diagnosis of ALS.

In response to the publication of “The El Escorial Criteria: Strengths and Weaknesses” (Chieia et al., 2010; Agosta et al., 2015), the WFN subgroup on ALS/MND initiated a revision of the El Escorial criteria in 2015. In the newest revision, which follows the El Escorial criteria for possible ALS as revised in 1998 and the Awaji criteria in 2008, the currently recognized, restricted phenotypes of ALS should be reconsidered for diagnosing ALS, and a diagnosis of ALS cannot be precluded when UMN and LMN lesions progressively extend in the course of the disease. In addition, it is suggested that cognitive impairment, sensory deficits, oculomotor systems, and sphincter disturbances might all be features of ALS, and there are multiple origins of fasciculation that are not always representative of LMN lesions (Ludolph et al., 2015). For these revised diagnostic criteria, we believe that prominent abnormalities of cognition, sensory nerve conduction, oculomotor systems, and sphincter function are likely to cause false-positive caution in the diagnosis of ALS, especially in early-stage ALS.

For the present diagnosis of ALS, there is a lack of clinical auxiliary diagnostic tests that are useful for this disease; thus, neurologists generally make an ALS diagnosis depending on the symptoms and signs of UMNs and LMNs in the same body area, accompanied by the evidence of disease progression to other regions (Brown and Al-Chalabi, 2017). The El Escorial Revisited introduced a combination of UMN and LMN symptoms and signs to establish levels of diagnostic certainty for ALS (Miller et al., 1999). Clinical trial investigators habitually enroll patients with either probable or definite ALS according to the 1998 revised El Escorial criteria, which highlights their universality. However, there may be problems with restrictiveness and sensitivity when ALS patients are enrolled according to these diagnostic criteria. For example, these criteria can have poor sensitivity, particularly in the early stages of ALS (Traynor et al., 2000b). Because of such limitations, these criteria have been revised to improve the

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sensitivity of early diagnosis (Ross et al., 1998) and optimize the diagnostic certainty and accuracy, particularly in the early stages of the disease, which are the most likely to benefit from therapeutic interventions for ALS patients in routine clinical practice (Beghi et al., 2002). Although functional and structural neuroimaging and neurophysiological and laboratory investigations can reduce the misdiagnosis of ALS (Simon et al., 2015), neurophysiological or neuroradiological findings are a common cause of uncertain diagnosis because of technological faults and defects (Davenport et al., 1996). In addition, a long time is often needed before a definitive diagnosis of ALS can be made, partially because of the insidious onset of symptoms and signs. Therefore, the median time for a definitive diagnosis is approximately 14 months (Chio, 1999).

Neurologists usually use a combination of clinical evaluation and laboratory examinations to successfully diagnose ALS. The error rate of ALS diagnosis in large general hospitals is < 10% (Davenport et al., 1996; Mills, 2010; Kiernan et al., 2011). Furthermore, the Scottish ALS registry has identified a false-positive rate of 8% (Davenport et al., 1996), and other data from population-based studies have reported similar false-positive rates, with false-negative rates approaching 44% (Belsh and Schiffman, 1996; Traynor et al., 2000a). In false-positive cases, the main reasons for revising a diagnosis include the non-appearance of disease progress, alterations in the development of atypical features, and negative results of follow-up neurophysiological and neuroradiological investigations (Davenport et al., 1996; Traynor et al., 2000a). Multifocal motor neuropathy is the most frequent disorder to be misdiagnosed as ALS, followed by Kennedy's disease (Traynor et al., 2000a; Kiernan et al., 2011).

Most ALS patients would go undiagnosed if the El Escorial Revised (Brooks et al., 2000) was used in the early diagnosis of ALS (Belsh and Schiffman, 1996; Traynor et al., 2000a), because the majority of ALS patients only present with clinical signs or symptoms in one or two regions, or present with pure muscle atrophy or only a lateral funiculus lesion. Moreover, ALS must be distinguished from a range of ALS-mimicking syndromes that have similar clinical manifestations to ALS in the early period (Johnsen et al., 2019). Because of the variety of diseases that can resemble ALS in the early stages, patients with a diagnosis of ALS should obtain a neurologist's opinion at regular intervals. Neurologists can then decide whether or not to change the diagnosis based on the alteration of symptoms and/or signs (Silani et al., 2011). In our experience, ALS patients who simultaneously present with the symptoms and signs of both muscle atrophy and lateral funiculus sclerosis are very rare in the early stages. We therefore believe that the accurate and early diagnosis of ALS is impossible without any reliable biomarkers (Kaur et al., 2016; Duan et al., 2020). The SOD1 gene on chromosome 21 was reported to play an important role in some cases of familial ALS in 1991, and noncoding repeat expansions in C9orf72 were then identified as a major cause of ALS in 2011. To date, however, there are no definitive diagnostic tests or genetic biomarkers for diagnosing ALS. The use of current technologies makes it very difficult to obtain an early and accurate diagnosis of ALS, and are likely to produce many false-negative and false-positive diagnoses of ALS.

The diagnosis of ALS depends mainly on patients' symptoms and signs as observed by neurologists, as well as on a series of clinical tests that are performed to rule out similar diseases. At present, there is no auxiliary clinical technique that can be used to make a definite diagnosis of ALS. The El Escorial criteria of ALS revised in 2015 strongly suggest that ALS patients must present with the symptoms and signs of UMN and LMNs in a single limb. Neurologists who obtain the patient's full medical history usually carefully conduct

a general neurological examination, assess UMN and LMN lesion symptoms (including the weakness, atrophy, and spasticity of muscles, and tendon hyperreflexia), and check for pathological signs (Xu et al., 2013), including the Rossolimo, Hoffmann, Babinski, Oppenheim, Gordon, Chaddock, Conda, Schaeffer, grasp, palmomentary, and sucking reflexes, which gradually become worse or appear at regular intervals.

Because a wide variety of diseases have similar symptoms and signs to ALS, and there is no specific confirmed biomarker for diagnosis, a diagnosis of ALS is based on inclusion and exclusion criteria. Appropriate routine differential diagnosis must be conducted to exclude the possibility of other similar diseases (Silani et al., 2011). Common differential diseases include multiple sclerosis, spinal cord tumor, syringomyelia, cervical spondylosis, post-polio syndrome, multifocal motor neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, spinal muscular atrophy, spinal and bulbar muscular atrophy, Lambert-Eaton syndrome, benign fasciculation syndrome, human immunodeficiency virus disease, human T-cell leukemia virus disease, Lyme disease, syphilis, tick-borne encephalitis (Hansel et al., 1995), and ALS-like genetic diseases. Auxiliary tests are an important method of differential diagnosis. For example, for the differential diagnosis of ALS, neurophysiological tests are essential. Routine tests include nerve conduction velocity (NCV) and EMG, whereas transcranial magnetic stimulation is less commonly used (Winhammar et al., 2005; Simon et al., 2015). EMG detects muscle electrical activity. Certain EMG findings can support an ALS diagnosis. In contrast, specific abnormalities of NCV may identify peripheral neuropathies or myopathies rather than ALS. NCV are essential for excluding disorders that are similar to ALS, such as demyelinating motor neuropathies. Multifocal motor neuropathy should show a conduction block in at least two motor nerves in NCV (Olney et al., 2003). However, the motor NCV is normal at the early stages of ALS, but compound muscle action potential amplitudes are reduced at the middle and late stages of the disease, indicating muscle denervation. Sensory NCV is also normal in the early stages of typical ALS, which can be used to differentiate ALS from demyelinated neuropathies (Eisen, 2001).

As well as NCV, EMG is very useful for identifying LMN lesions. The features of EMG that show LMN loss include fibrillation potentials, positive sharp waves, and chronic neurogenic changes (Eisen and Swash, 2001; de Carvalho et al., 2008). These abnormal EMG findings have all been incorporated into the El Escorial criteria of ALS revised in 2015. EMG can be used to detect pre-clinical, sub-clinical, or potential lesions involving LMNs, because fibrillation potentials and positive sharp waves can be detected in muscles that seem clinically normal (Eisen and Swash, 2001). EMG findings can therefore help to make an early diagnosis of LMN lesions by detecting fibrillation potentials and positive sharp waves. In addition, the partial survival of motor units in muscles with larger partial motor neuron death can produce fasciculation potentials, which are clinically visible as twitching in the involved muscle; this is a typical feature of ALS (Gubbay et al., 1985). The detection of fasciculation potentials in the tongue is highly specific for diagnosing ALS (Li et al., 1986). Furthermore, fasciculation potentials in ALS are complex and malignant signs that represent re-innervation, which have a diagnostic importance for MRI when combined with chronic neurogenic alterations. MRI is another important auxiliary examination that can be used to differentiate brain and spinal diseases that are similar to ALS. A muscle biopsy can also be performed to eliminate the possibility of most muscle diseases, and can further exclude some unusual myopathies such as polyglucosan body disease, or confirm the presence of ALS based on the presence of atrophy of mixed-fiber type muscles (Baloh et al., 2007). We also propose that

a genetic test should be routinely conducted to exclude ALS-like genetic diseases in the differential diagnosis of ALS; this is especially important for the early diagnosis of ALS. In cases of pure LMN lesions, a genetic test is an important measure for differentiating Kennedy's disease, X-linked bulbospinal atrophy, and spinal muscular atrophy (Rocha et al., 2005).

With developments in EMG technology, most potential or pre-clinical LMN lesions can be accurately identified by EMG (Bokuda et al., 2020). However, although transcranial magnetic stimulation, voxel-based morphometry, and diffusion tensor imaging can be used to detect lateral funiculus lesions, there remains a need for useful and objective auxiliary tests that can detect lateral funiculus sclerosis in surviving ALS patients. Additionally, the neuroimaging technologies that can be used to detect the lateral funiculus are currently limited, especially for the brainstem and spinal cord. We therefore believe that the early, accurate, and definite diagnosis of ALS is very difficult. The identification of reliable diagnostic biomarkers is a very feasible possibility for overcoming this difficulty. The scheduling of follow-up appointments after the initial diagnosis is also necessary, because this can help to provide more information for the definitive diagnosis of ALS (Andersen et al., 2007).

In conclusion, ALS is the pathological name of the disease, because its typical pathological changes include irreversible, chronic, progressive, and selective death of the cerebral, spinal and/or brainstem UMNs and LMNs that control voluntary muscles, and the accompanying sclerotic changes in the corticospinal lateral tract (Kiernan et al., 2011; Zarei et al., 2015; Riva et al., 2016). In contrast, MND is a group of diseases that are characterized by the irreversible, chronic, progressive, and selective death of UMNs or LMNs. MNDs are traditionally divided into four subtypes according to clinical manifestations. Of these, ALS is considered the commonest subtype; the other three subtypes are PLS, PMA, and PBP (Raman et al., 2015). The current doubts around the concept and definition of ALS are because ALS is acknowledged to not only involve UMN and LMN lesions, but also to involve neuronal lesions associated with deficits in cognition, sensory nerve conduction, oculomotor systems, and sphincter function, especially in the middle and later stages of ALS. If we continue to use the current concept and definition of ALS in clinical and research work, it is likely to produce misunderstandings, because ALS is defined as a disease that merely damages UMNs and LMNs. Moreover, ALS cannot currently be diagnosed if it is accompanied by lesions in non-motor neurons.

Furthermore, it is inappropriate to consider ALS as a subtype of MND, because MND is a group of diseases that only damage motor neurons, and not non-motor neurons. Moreover, according to the 2015 revised El Escorial criteria, the other three subtypes of MND might merely be different onset types or stages of ALS (Ludolph et al., 2015). Most MNDs may ultimately involve damage to both UMNs and LMNs, and develop into ALS. To date, there is no clear evidence about whether or not the different subtypes of MND are independent diseases, each with an independent pathogenesis. Therefore, the concept and definition of ALS, including MND, need to be further clarified.

The current diagnostic criteria of ALS (Ludolph et al., 2015) mainly depend on clinical manifestations, and aside from EMG, there are no objective auxiliary technologies for the diagnosis of this disease. Other examination methods, including computed tomography, MRI, and some laboratory tests, are generally used for differential diagnosis only. Moreover, EMG only detects LMN damage, and is not sensitive or definitive for identifying UMN damage. Although some findings have been reported about detection methods for UMN damage, including functional MRI and positron emission tomography

(Huynh et al., 2016), these can only partially examine lesions in the corticobulbar and corticospinal tracts in the cerebrum, and have very limited use for identifying such lesions in the brainstem and spinal cord, or for identifying motor neuron lesions in the motor cortex. An objective neuroimaging diagnostic method for lesions in UMNs, and especially of lateral funiculus sclerosis, has not yet been found. Present neuroimaging methods can only detect reductions in the corticobulbar and corticospinal tracts in the cerebrum, but cannot detect lateral funiculus sclerosis scars. Therefore, the current estimation of UMN lesions mainly depends on patients' clinical manifestations, including elevated muscle tension, hyperfunction of tendon reflexes, and pathological signs.

Although Ludolph et al. (2015) proposed that LMN lesions, as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, or lumbosacral), are one of the ALS diagnostic criteria, this criterion is unable to completely exclude partial PMA and PBP from ALS, and greatly increases false-positive diagnoses of ALS. However, if UMNs and LMNs are simultaneously damaged, it is necessary for diagnosing ALS. Nonetheless, with these diagnostic criteria, the diagnosis of some types of ALS can be problematic, and ALS may be missed in some patients. For example, ALS may be missed in patients who develop LMN damage followed by UMN damage, because the LMNs in a certain body region are seriously damaged, and then the UMNs begin to be damaged. In this case, the clinical manifestations of tendon reflex hyperfunction and pathological signs would be unable to be detected because of blocked reflex arcs. Because potential UMN damage cannot be identified in this type of ALS, the current diagnostic criteria are not adaptive and would increase the false-negative diagnosis of ALS. This may be one reason why the false-negative rate of ALS diagnosis can be up to 44% (Belsh and Schiffman, 1996; Traynor et al., 2000a). Therefore, some problems remain with regard to the diagnosis of ALS.

Strengths and Limitations

This review provides practical information for best practice in uniform investigation and treatment strategies, based on current literature and author opinions from their clinical experiences with adult ALS. This review will increase the awareness of ALS among neurologists and help to improve the diagnosis and treatment of such patients. Moreover, the increasing economic burden of ALS has recently been highlighted. Clear guidance will help to educate attending doctors to manage these patients appropriately, which will reduce the use of excessive laboratory tests and promote the early treatment of ALS. There are a number of ongoing clinical trials regarding ALS (<https://www.clinicaltrials.gov/>). With the development of medical management and diagnostic technologies, the concept, definition, and diagnosis of ALS may be updated in time.

There are some limitations to this review. Only peer-reviewed literature in English was included, which limits the scope of this review. Another limitation of this study is that, rather than being based on expert consensus and high-quality prospective research, the views of this paper are mainly based on the literature retrieved at the time of searching, and on some problems noted by the authors in their clinical work.

Conclusion

The concept, definition, and diagnostic criteria of ALS leave some room for doubts, and can cause difficulties for neurologists in the clinical treatment of ALS. The concept, definition, and diagnostic criteria of ALS should therefore be comprehensively discussed. Because autopsy is the gold standard of ALS diagnosis, further investigation should focus

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on identifying reliable biomarkers—especially neuroimaging biomarkers—through autopsy for the diagnosis of lateral sclerosis. Diagnostic delay and missed diagnosis can delay appropriate drug treatments. In addition, misdiagnosis can lead to the use of inappropriate therapies, causing serious psychosocial and emotional burdens for patients and their families. Moreover, unclear diagnoses can introduce inaccuracies into clinical and basic research on ALS. It is therefore necessary to standardize the concept and definition of ALS, and to identify sensitive and definitive diagnostic criteria for this disease.

Despite the limitations of our literature- and clinical experience-based method, this review reflects an up-to-date concept, definition, and diagnostic criteria of ALS, which will help to guide neurologists and serve their patients. High-quality retrospective and prospective studies are required for all of the areas of uncertainty that were highlighted in this review, to improve the clinical diagnosis and treatment of ALS patients.

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