Amyotrophic lateral sclerosis: moving towards a new classification system

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Amyotrophic lateral sclerosis is a progressive adult-onset neurodegenerative disease that primarily affects upper and lower motor neurons, but also frontotemporal and other regions of the brain. The extent to which each neuronal population is affected varies between individuals. The subsequent patterns of disease progression form the basis of diagnostic criteria and phenotypic classification systems, with considerable overlap in the clinical terms used. This overlap can lead to confusion between diagnosis and phenotype. Formal classification systems such as the El Escorial criteria and the International Classification of Diseases are systematic approaches but they omit features that are important in clinical management, such as rate of progression, genetic basis, or functional effect. Therefore, many neurologists use informal classification approaches that might not be systematic, and could include, for example, anatomical descriptions such as flail-arm syndrome. A new strategy is needed to combine the benefits of a systematic approach to classification with the rich and varied phenotypic descriptions used in clinical practice.

Introduction

The description of amyotrophic lateral sclerosis (ALS) as a progressive neurological disease in which upper and lower motor neurons degenerate, leading to relentlessly worsening paralysis of voluntary muscles until death ensues,[1] is a definition that most neurologists would recognise. However, because of the great clinical variability in presentation and prognosis, the generation of a systematic, consistent description of clinically defined subtypes is not straightforward.[2] Nevertheless, a classification system for ALS that includes diagnostic criteria and phenotype at the time of diagnosis (clinical presentation) and as the disease progresses (clinical subtype) would be important to help guide treatment, provide an indication of prognosis, and enable analysis in clinical trials of homogeneous groups for a more personalised approach to therapy, and would be valued by patients and their families.

There is no definitive diagnostic test for ALS, and confirmation of diagnosis is based on clinical findings, electromyography results, and exclusion of mimics. The same is true for phenotypes since no biomarkers are available to distinguish them. This absence of biomarkers can lead to inconsistency when subtypes are defined, because they can be arbitrarily assigned as a new disease or as an extension of the existing ALS spectrum (figure 1). The blurring of the boundary between diagnosis and phenotypic description is particularly apparent in the example of the upper motor neuron disease primary lateral sclerosis (PLS) and the lower motor neuron disease progressive muscular atrophy (PMA), which were initially regarded as separate entities,[3,4] but were subsequently considered different manifestations of the same condition,[5] described by the term motor neuron disease[6] in the UK and some other countries and ALS in the USA and elsewhere. This grouping of three different clinical phenotypes (ALS, PLS, and PMA) into a unifying diagnosis (motor neuron disease or ALS), on the basis of clinical symptoms caused by degeneration of different components of the motor system, has been used by clinicians for over 50 years. However, a key difficulty remains as to whether PLS and PMA are distinct diseases or part of the spectrum of ALS,[7] and therefore whether ALS comprises several degenerative motor neuron diseases (figure 1).[8–12]

The difficulty arising from the use of ALS both as an overarching diagnostic term meaning degenerative motor neuron disease and as a description of a specific subtype of degenerative motor neuron disease has been compounded by use of the terms bulbar palsy, pseudobulbar palsy, and progressive bulbar palsy to describe anatomically circumscribed patterns of ALS, PLS, and PMA confined to musculature controlling speaking and swallowing, and terms such as flail-arm or flail-leg syndrome to describe anatomically distinct patterns, since these descriptions mix anatomy, neural level, and clinical presentation.

The problem of classification is further complicated by the rapid increase in knowledge of genetic causes, a deeper understanding of the non-motor manifestations of ALS, and the discovery of pathological subtypes, all of which overlap partly but not neatly with the clinical presentations.[13]

In this Personal View, we summarise the phenotypes of ALS based on different approaches to classification, and show that existing classifications are inconsistent and do not enable accurate description of ALS phenotypes. We highlight the challenges raised by advances in our understanding of the disease, including a growing appreciation of extramotor features of ALS, identification of genetic subtypes, and the potential role of biomarkers. Finally, we use the latest research findings to propose a systematic approach to classification, designed to convey relevant information while being simple to use, yet remaining flexible enough to incorporate new research findings.

Current diagnostic and phenotypic classification

Classification with the El Escorial criteria and its revisions[14–17] is the approach with the greatest agreement among experts. These criteria were developed for research purposes, but in the absence of a confirmatory

diagnostic test for ALS they are commonly used in clinical diagnosis (table 1). Classification with the International Classification of Diseases (ICD) is also in widespread use through hospital coding systems. Finally, each clinician has their own idiosyncratic, personal classification system, based on a selection of the terms available for diagnosis and phenotype, used for everyday interactions with patients.[2]

The El Escorial diagnostic criteria

The El Escorial criteria were developed by the World Federation of Neurology Research Group on Motor Neuron Diseases to define research-based consensus diagnostic criteria; these criteria, published in 1994, subsequently underwent revisions known as the Airlie House criteria and the Awaji-Shima criteria.[14–17]

According to the El Escorial criteria, diagnosis of ALS depends on identification of upper and lower motor neuron signs within body regions defined as bulbar, cervical, thoracic, and lumbar.[14–16] In the original criteria, there were four levels of diagnostic certainty ranging from suspected ALS to definite ALS (table 1).[14] The levels of diagnostic certainty depended on clinical assessment of the extent and distribution of upper and lower motor signs, supplemented by neurophysiological (electromyography and central motor conduction time) and imaging (MRI, CT, and PET) data to exclude ALS mimics.

In 2000, the El Escorial criteria were revised to improve diagnostic sensitivity, by removing the "suspected" category and adding a "laboratory-supported probable ALS" category (table 1).[15] Although the resulting Airlie House criteria were specific for ALS, sensitivity remained a challenge, particularly in the early stages of the disease, resulting in substantial diagnostic delay and limiting recruitment of patients with ALS into therapeutic trials.[18–20]

The 2008 revision, the Awaji-Shima criteria,[16] incorporated a recommendation to use electrophysiological data in the diagnosis of ALS. Specifically, neurophysiological features of lower motor neuron dysfunction, including acute changes such as fibrillation potentials and chronic neurogenic changes such as unstable motor units, were considered to be equivalent to clinical features of lower motor neuron dysfunction. Separately, fasciculations were also identified as features of active denervation, with morphology used to define ALS-specific fasciculations.

The diagnostic usefulness of the Awaji-Shima criteria and the Airlie House criteria have been compared in single-centre studies, which have mostly reported a higher sensitivity with use of the Awaji-Shima criteria.[17,21–28] This increased diagnostic accuracy is most apparent in cases of bulbar-onset ALS.[23,29] The El Escorial criteria and its revisions are, however, limited in scope and not suitable for all applications. For example, a patient could be classified as having possible ALS when neurologists would have no doubt about the diagnosis because clinical findings have led to exclusion of all other explanations. This discrepancy between classification with the El Escorial criteria and clinical diagnosis can lead to confusion in communication with patients.

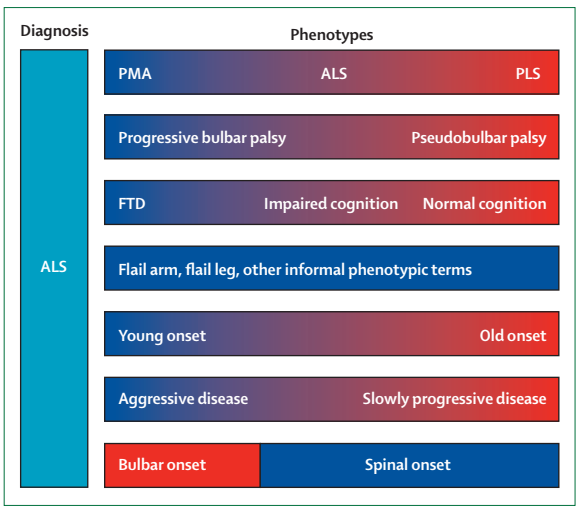

Figure 1: **Diagnosis and phenotypes of amyotrophic lateral sclerosis**
The term amyotrophic lateral sclerosis (ALS) is an overarching diagnosis, and is used interchangeably with motor neuron disease in the UK and some other countries. The term ALS is also used to distinguish the ALS phenotype from progressive muscular atrophy (PMA), primary lateral sclerosis (PLS), and other clinical manifestations. Whether PLS and PMA should be regarded as phenotypes of ALS or as diseases in their own right is not clear. The terms bulbar palsy and pseudobulbar palsy are sometimes used as diagnoses, but they are actually phenotypes of ALS. Cognitive impairment presents as a continuum but criteria define a cut-off for the diagnosis of frontotemporal dementia (FTD). Whether ALS–FTD should be regarded as a phenotype of ALS or as a diagnosis is also not clear. Flail arm, flail leg, and other terms are used to describe specific patterns of symmetrical limb weakness that are seen fairly frequently. Cut-offs for other continuous variables, such as age of onset and disease progression, are not defined by existing criteria. Bulbar onset accounts for about 25% of cases of ALS; bulbar onset and spinal onset can occur simultaneously, and other sites of onset, such as respiratory muscles, are sometimes seen.

Moreover, the term ALS is used in clinical practice both as a diagnosis and to describe a particular phenotype distinct from PMA, PLS, bulbar palsy, and other clinical presentations. The El Escorial diagnostic criteria and their revisions describe the certainty that the phenotype is ALS as opposed to PMA or PLS—ie, the terms possible, probable, and definite refer to the severity of clinical presentation as a result of the pathology involved, and not to the underlying diagnosis of ALS.

Classification for clinical coding

The ICD coding system is a method that allows mortality and morbidity statistics to be compared across institutions and countries, and should reflect a systematic description of each disease and its subtypes, although categories can be arbitrary. The ICD is revised on a regular basis to reflect changes in understanding of disease, and the current version, ICD-10, is undergoing revision, with a final version of ICD-11 expected for approval by the World Health Assembly in 2018. ICD-11 will include definitions of each term and links to the Systematized Nomenclature