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ORIGINAL ARTICLE

The El Escorial criteria: Strengths and weaknesses

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Abstract

The El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis (ALS) were established 20 years ago and have been used as inclusion criteria for clinical trials. However, concerns have been raised concerning their use as diagnostic criteria in clinical practice. Moreover, as modern genetics have shed new light on the heterogeneity of ALS and the close relationship between ALS and frontotemporal dementia (FTD) recognized, the World Federation of Neurology Research Group on ALS/MND has initiated discussions to amend and update the criteria, while preserving the essential components for clinical trial enrolment purposes.

Key words: *ALS, El Escorial*

Introduction

The El Escorial criteria were developed to generate a common understanding of diagnostic procedures for amyotrophic lateral sclerosis (ALS) (1) and were subsequently revised in Airlie House in 1999 (2). Although the criteria have been repeatedly shown to be specific with respect to the diagnosis of ALS, their recognized limitations have led to calls for revision. It is a general understanding that 1) these criteria build a basis of a formal framework for the diagnosis of ALS; 2) they are useful as a basis for the conduct of clinical trials, in particular with regard to inclusion and exclusion criteria; and 3) they play a useful role for access to health care systems worldwide.

There has been an additional debate relating to the utility of the recently enunciated Awaji criteria (3) as a means to refine the El Escorial criteria, including challenges with respect to the availability worldwide of sophisticated electrophysiological techniques.

Members of the World Federation of Neurology (WFN) Research Group on ALS/MND met to discuss the El Escorial criteria in December 2012, and have generated a discussion document outlining the preferred approach to criteria modification.

Usefulness of the El Escorial criteria in the clinic

Criteria for diagnosis of amyotrophic lateral sclerosis (ALS) emerged in the late 1980s to facilitate inclusion of patients into large multicenter clinical trials. Accordingly, the impact of these criteria has been in greater evidence in clinical research than within clinical practice. The initial goal of the El Escorial criteria was to standardize steps of the diagnosis, clarification of the complexity of the various clinical features, and to ensure diagnostic certainty. With time (1,2,4) there was need to simplify the criteria

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from five levels (suspected, possible, laboratory-supported probable, probable and definite ALS) to three (possible, probably and definite ALS). The literature before and after the publication of the El Escorial criteria does not prove that the criteria provided a clear gain regarding either the accuracy of the diagnosis (false-negative: 37% before, 30% after), or diagnostic delay (12 months before, 11 months after) (5–7).

Moreover, the heterogeneity of ALS based on clinical phenotyping was not addressed by these criteria, as many centers have continued to use older phenotypic descriptions including flail arm, flail leg, primary lateral sclerosis, or pure bulbar palsy, which are considered to provide richer clinical information than terms such as definite, probable or possible ALS. Revised criteria should facilitate the inclusion of specific phenotypes that ultimately reflect the disseminated neuropathological process.

Clinical trials: early diagnosis and the El Escorial criteria

The use of the El Escorial criteria as inclusion criteria for clinical trials

Both the original and revised El Escorial criteria have been employed as inclusion criteria for clinical trials. Prior to 2010, the vast majority of trials restricted enrollment to subjects meeting criteria for definite, probable, or laboratory-supported probable ALS (8–16). Other criteria for inclusion varied widely in these trials, including phenotypic and prognostic information such as vital capacity and duration of symptoms. More recently, a number of trials have permitted inclusion of possible ALS as an entry criterion (17,18). Erroneous diagnosis does not seem to be increased in these trials; only five of 952 enrolled subjects for the study of dexpramipexole in ALS were subsequently found to have alternative diagnoses, well within the range of previously published trials (Kerr, personal communication).

The addition of possible ALS as an inclusion criterion means that subjects with clinical signs limited to one body region are eligible for clinical trials. It is difficult to conceive of a less stringent criterion that would still ensure that patients were appropriately diagnosed. Recent ALS trials evaluating potential disease modifying treatments have prioritized patients with early disease, and given the low diagnostic error rate noted with inclusion of possible, probable, laboratory- supported probable, and definite ALS, it appears that the current criteria meet the needs of those designing clinical trials now and in the future. One possible exception would be trials of agents whose targets are specific and known gene mutations; in such cases, clearly patients with only the appropriate mutation should be eligible. Given our current understanding of the role of single gene mutations in ALS, the definition of familial ALS (19) and the uncertainty regarding the possibility of oligogenic pathogenesis, it is clear that inclusion of genetic factors in ALS criteria is as yet unjustified. Thus, from a clinical trial perspective the existing criteria, with minor modifications, remain fit for purpose.

Use as prognostic modifier

It is important to note that the El Escorial criteria were conceived as a system to establish a clear diagnosis and not as a staging system. However, given that the major differences between definite, probable, and possible ALS involve the number of body areas affected by the disease, some investigators have evaluated the extent to which initial diagnosis impacts prognosis. Turner et al. (20) evaluated more than 800 patients diagnosed with ALS over a 10-year period in a large multidisciplinary ALS clinic, and found that initial diagnosis was significantly related to outcome both in a univariate and multivariate analysis. The main difference in outcome was between those patients initially involved with definite ALS and all others. Similarly, Chio et al. (21) evaluated a population based prospective cohort of 221 patients, and noted that while patients with probable or possible ALS had nearly identical survival rates, patients with an initial diagnosis of definite ALS fared significantly worse. These studies raise the possibility that stratification of patients along El Escorial diagnostic categories, and with other recognized prognostic indicators, could prove useful in reducing variability in future ALS trials.

Is the spectrum of ALS represented in the El Escorial criteria?

While it is acknowledged that the El Escorial criteria have been valuable in facilitating standardization of diagnostic criteria for entry into clinical trials and clinical research studies, there has been considerable evolution in our understanding of phenotypic heterogeneity and prognostic indicators since the criteria were established.

Common reasons why patients fail to meet clinical trial entry criteria include:

- Respiratory function too impaired;
- Slow disease progression, with onset of symptoms >3 years previously;
- Patient requires gastrostomy feeding or non-invasive ventilation;
- Patient has a pure lower motor neuron disorder (progressive muscular atrophy (PMA));
- Disease features are isolated to one segment, e.g. progressive bulbar palsy (PBP).

Early revision of the El Escorial criteria included a category of clinically probable laboratory- supported ALS (2) – allowing the sensitivity of electromyography (EMG) to detect subclinical denervation reflecting lower motor neuron (LMN) pathology. However

patients with clinically possible ALS continued to be excluded from trials. Such patients may have UMN and LMN signs in one region, MN signs alone in two regions, or LMN rostral to UMN signs. Perhaps the most powerful argument for inclusion into clinical trials is for those patients with progressive muscular atrophy (PMA) and progressive bulbar palsy (PBP). The disease course of patients with PMA is often very similar to classical ALS (22); many PMA patients develop UMN signs during the course of the disease and at least 50% of patients clinically diagnosed with PMA have corticospinal tract pathology at autopsy (23). Moreover, there is substantial clinical (PMA and ALS within the same family), genetic, neuroimaging and pathological evidence that there is substantial overlap between ALS and PMA (33,36–41). On the other hand, before the diagnosis of PMA is made, potential mimic syndromes should be excluded (42). Other lower motor neuron presentations that may be even more difficult to differentiate from PMA/ALS are the segmental spinal muscular atrophies which have a benign prognosis if still segmental after four years of follow-up.

It may help to differentiate pure lower motor neuron disease from PMA/ALS if we had a reliable biomarker for upper motor neuron loss that might facilitate the diagnosis of ALS in the future.

However, given the current lack of good biomarkers for UMN involvement, it seems reasonable that a practical diagnosis of ALS can be made with clinical features of LMNs alone, even without clinical features of UMNs, on condition that their progress in degree and expansion to other body parts are compatible with the experience of ALS specialists.

In progressive bulbar palsy, the patient may present with a spastic dysarthria without LMN signs initially being detectable clinically or on EMG. It is accepted that that PBP patients who have been properly investigated almost universally turn out to have ALS.

Accordingly, there is a clear need to carefully revise and evolve the criteria to permit categorization of patients with PMA and PBP vs. ALS/MND variants, and to permit their inclusion into trials.

Of the other subphenotypes, patients with the flail arm and the flail leg phenotype or the UMN disorder of primary lateral sclerosis (PLS) frequently have a more benign disease course, rendering assessment of therapeutic efficacy of potential neuroprotective agents more difficult to discern. However, given that the current consensus is that these clinical phenotypes are variants of the same pathological process as ALS, such patient subgroups should not be excluded from access to proven neuroprotective agents.

Electrophysiology and early diagnosis of ALS: Awaji criteria

The diagnosis of ALS is based on clinical criteria. However, EMG and other electrodiagnostic measures may increase diagnostic sensitivity. The Lambert criteria for EMG diagnosis of ALS were incorporated into both the original and revised El Escorial criteria. However, these criteria are now recognized as being insensitive and incomplete (3). In addition, to be judged suggestive of ALS, any muscle studied by EMG must show both motor unit remodelling and ongoing denervation. This stringent criterion lessens the potential contribution of EMG to early diagnosis.

To meet the need for early diagnosis for therapeutic trials, the International Federation of Clinical Neurophysiology (IFCN) sponsored a consensus meeting in Awaji Island, near Tokushima in Japan 3–5 December 2006 (3).

A number of the follow-up studies on the Awaji criteria have shown significantly increased sensitivity for early diagnosis (3,24–26), suggesting that these should be adapted as part of the overall modification of the El Escorial criteria.

Imaging and the individual diagnosis of ALS

The use of routine magnetic resonance imaging (MRI) of the brain and spinal cord in patients suspected of having a motor neuron disease (MND) is recommended to exclude other causes of signs and symptoms of MN pathology ('exclusion' features) (27). The detection of corticospinal tract (CST) hyperintensities on conventional MRI and a T2-hypointense rim in the precentral gyrus can support a pre-existing suspicion of MND ('supportive' feature). However, the specific search of these abnormalities for the purpose of making a firm diagnosis of MND is not recommended (27).

Over the past 10 years, there have been significant advances in the identification of neuroimaging patterns in MND (28). As in other neurodegenerative conditions (e.g. Alzheimer's disease (29), frontotemporal dementias (30), new criteria should acknowledge the value of these (supportive) features. In the absence of definitive biomarkers of upper motor neuron (UMN) involvement, a significant cortical thinning of the precentral gyrus (31), damage to the CST and corpus callosum assessed using diffusion tensor MRI (32,33), and altered N-acetylaspartate levels in the primary motor cortex and CST (36) should be considered consistent with MND ('supportive' criteria) and hold promise for assessing the UMN involvement before clinical symptoms become apparent.

Importantly, DTI (diffusion tensor imaging) MRI measures of the CST have a prognostic value in amyotrophic lateral sclerosis patients (34,35). Furthermore, patterns of brain damage are emerging to identify patients prone to develop dementia or have a rapid progression (28). It is strongly advisable to incorporate measures derived from advanced MRI techniques into new clinical trials as exploratory outcomes. This will provide additional insights into the

value of these techniques in the assessment of MND in the individual patient, and will contribute towards validation in the context of multicenter longitudinal studies.

The relation of FTD and ALS and the El Escorial criteria

The importance of extramotor manifestations of ALS, notably cognitive and behavioral impairment, was not fully acknowledged at the time of the original El Escorial criteria. The presence of dementia was originally classified as an exclusion criterion for ALS. This is now known to be incorrect. Although dementia has been recognized as a feature of ALS since the 19th century (50), the presence of cognitive involvement has been under-recognized in the past due to difficulties in performing extensive neuropsychological testing, particularly in later stages of ALS. With the advent of improved neuropsychological testing, it is now recognized from population based studies that up to 60% of those with ALS have some evidence of cognitive and behavioral impairment (51–53). The clinical presentation of extramotor involvement is underpinned by neuroimaging and neuropathology, which demonstrate involvement of frontal, temporal and deep gray matter regions (54,55). The importance of extramotor involvement in ALS is also underlined by the finding that in a recent thorough neuroanatomical and neuropathological study, only nine out of 86 brains lacked TDP-43 neuropathology of major areas that are cognitively relevant (55).

Consensus criteria have been proposed to categorize the various forms of cognitive and behavioral impairment associated with ALS (56), but further adjustments to reflect non-executive impairment, deficits in theory of mind and social cognition are required (57). A robust screening test for cognitive impairment in ALS has recently been validated across Europe and the US (57).

However, these exciting developments do currently not influence the formal diagnosis of ALS, which continues to rest on the presence of a motor system degeneration involving upper and lower motor neurons. Revisions of existing diagnostic criteria will benefit from inclusion of additional phenotype data, established using the currently developed tests, to enable stratification of those with cognitive deficits in future clinical trials.

The definition of familial ALS

The current version of the El Escorial criteria (1,43) does not take into account the presence or absence of a family history in defining the certainty of ALS as a diagnosis. At the time of design, only one Mendelian inherited gene (*SOD1*) was known to be associated with ALS, and the presence of a known disease-causing variant in this gene permitted a diagnosis of ALS in symptomatic individuals. However, within the past decade there has been a veritable explosion in ALS genetics. An important question to consider now is whether incorporation of genetics into diagnostic criteria would be useful.

A strong argument is that a positive family history of ALS must surely improve the reliability of diagnosis in a family member subsequently diagnosed with a progressive neurogenic weakness without sensory involvement. The issue is not, however, straightforward. Part of the problem is that the definition of 'familial' ALS depends on several components.

First, the definition of 'familial' depends on the neurologist (19), and while everyone might agree that three affected first-degree relatives constitutes a definite familial ALS pedigree, there is less consensus when there are only two affected, or when the other affected relatives are second or third degree.

Second is the issue of how accurately other family members are identified as having been affected by the proband, and the related problem of family members who are not yet affected but will be. One study showed that the risk to siblings of someone with apparently sporadic ALS is increased eight-fold (44), suggesting that misclassification rates are high.

Thirdly, the very use of the word familial is itself ambiguous. Familial does not mean genetic, since shared environmental factors are familial. Also, vertically transmitted diseases may appear inherited, compounding the problem.

Fourthly, ascertainment bias influences how often a second family member will be detected as affected. Large families, or those in which high penetrance genes are responsible for ALS, or those with genes associated with a younger onset of ALS, are all statistically more likely to have more than one first-degree relative affected. Furthermore, a family history of a different but related condition, such as frontotemporal dementia, may not be taken as a positive family history, and even if recognized, the full extent of ALS-related diseases is not yet known. Simple statistical modeling shows that for a gene with 70% penetrance, a pedigree with five children and a carrier parent will look familial 82% of the time, while a pedigree with two children will look familial just 50% of the time (45).

Finally, the familial ALS classification is itself outdated. Many phenotypes do not currently meet the criteria for diagnosis of typical ALS. For example, mutations in the *ALS2* gene result in a very young onset, almost exclusively upper motor neuron and very slowly progressive disease. Furthermore, many ALS genes cause other phenotypes either in the person with ALS (e.g. frontotemporal dementia) or in other family members (46–48) or ALS may be an uncommon manifestation of mutation in that gene even though when it occurs it is a typical, adult-onset, progressive mixed upper and lower motor neuron syndrome (49).

Thus, while it seems obvious that a family history of ALS should increase the certainty with which we diagnose ALS, a precise definition of 'familial' needs to be incorporated, along with a discussion as to how much weight a family history of other conditions such as frontotemporal dementia should carry. A good starting point is to define familial as suggested by research (19) with internationally agreed consensus. The term 'familial' should be differentiated from 'inherited' or 'genetic' ALS in usage, and the existing familial ALS classification should be overhauled with international agreement to reflect the phenotypes generated by mutations in the different ALS genes.

Summary, conclusions and further steps

Diagnostic criteria for ALS remain important for clinical trials, biomarker studies, genetic correlation, and other epidemiological studies. The El Escorial criteria have served the ALS community well in this regard. However, as our knowledge of the disease has expanded, there is room for modification to reflect the requirements of 21st century clinical research. These include the following:

Subphenotypes

Better clinical definitions of well-established subphenotypes (to improve inclusion of defined subgroups into clinical trials and to support access to health care systems). We need operative criteria for diagnosing subphenotypes and they should be included in a future revision of the El Escorial criteria. The presence and implications of cognitive and behavioral impairment in ALS requires further discussion and analysis by a working group of the WFN ALS/MND Research Group.

Staging

Although the El Escorial criteria were not intended to be used as staging or prognostic indicators, the presence of 'definite ALS', signifying an extensive burden of disease has been established as a negative prognostic indicator. New proposals for staging should be directly compared to the existing criteria.

Neurophysiology

The Awaji criteria improve sensitivity but the required technology is not universally available. The challenge will be to determine the extent to which these criteria should be included as part of the core clinical diagnostic criteria.

Genetics

A standard classification of Familial ALS should be adopted, and incorporated into the revised criteria. The presence of frontotemporal dementia in a family member should be included as a variant for the purposes of defining familial ALS.

Imaging

Imaging technology is developing rapidly, but is not yet suitable for individual patient analysis. However, it is likely that within the coming decade detailed signal analysis will permit at improved classification. Revised criteria should be sufficiently flexible to incorporate this evolving technology.

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