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Opinion Paper

A proposal for new diagnostic criteria for ALS

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1. Background

The El Escorial criteria for the diagnosis of Amyotrophic Lateral Sclerosis (ALS) were initially published in 1994 (Brooks, 1994) and revised in 2000 (Brooks et al., 2000). Criteria were established because the "variety of clinical features which may be present early in the course of ALS makes absolute diagnosis difficult and compromises the certainty of diagnosis for clinical research purposes and therapeutic trials." (Brooks, 1994) The original criteria described 4 categories of disease: Definite, Probable, Possible, and Suspected ALS. However, subsequent clinical experience made it clear that non-Definite categories included patients who would ultimately die of ALS with a high degree of clinical certainty. To increase diagnostic sensitivity, the revised criteria (Brooks et al., 2000) included a category called "laboratory-supported probable ALS" that allowed the use of Electromyography (EMG) data to substitute for clinical findings, and the category of "suspected ALS" was deleted. While the remaining categories identified patients with ALS with a high degree of specificity, many clinical neurophysiologists were concerned that sensitivity was compromised because of the specific way EMG data contributed to the diagnosis and noted that fibrillation-sharp wave potentials, defined as an obligatory lower motor neuron sign, were often absent in otherwise affected muscles (de Carvalho et al., 1999). To address these perceived problems, the Awaji criteria (de Carvalho et al., 2008) modified the revised El Escorial Criteria to further integrate electrophysiological criteria with clinical examination findings, and to add the presence of fasciculations as a lower motor neuron sign that could substitute for fibrillation potentials-positive sharp waves in muscles with neurogenic changes. The Awaji criteria

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eliminated the category of 'laboratory-supported probable ALS', but maintained the definite, probable, and possible categories.

Many studies performed subsequent to the publication of the Awaji criteria have demonstrated that use of these criteria modestly improves the sensitivity of diagnosis of ALS as compared to the revised El Escorial (Gawel et al., 2014; de Carvalho, 2012; Boekestein et al., 2010). Some studies have suggested a loss of sensitivity due to the Awaji Criteria eliminating the diagnostic category of Laboratory Supported Probable ALS; however, this is primarily due to the fact that some patients were moved from Laboratory Probable ALS to Possible ALS (Higashihara et al., 2012). Possible ALS is in fact a definitive diagnosis, so that having an increased number of patients so diagnosed does not truly represent a loss of sensitivity. A recent multicenter study comparing criteria has reaffirmed the increased sensitivity attained when the Awaji Criteria are employed (Johnsen et al., 2019).

However, both the revised El Escorial and the Awaji criteria are complex to apply and prone to error. A recent multicenter study of inter-rater reliability of diagnoses made based on the Awaji and revised El Escorial criteria presented clinical and electrophysiological data from nearly 400 patients being evaluated for ALS to 8 neurophysiologists of variable experience in ALS; test–retest reliability was quite low for both criteria, with the diagnoses of "not-ALS" and "Definite ALS" showing better agreement than probable or possible ALS, in particular when applying Awaji criteria (Johnsen et al., 2019).

A second limitation to both the revised El Escorial criteria and the Awaji revision relates to the multiple categories of ALS that are defined. Definite, Probable, or Possible ALS are understandably interpreted by patients and clinicians as assessments of the likelihood that ALS is in fact the disease causing the symptoms the patient is experiencing. However, all three categories describe patients whose disease is in fact ALS, to a very high degree of diagnostic certainty. There is also no clear implication that patients with possible ALS will evolve through the categories of probable and definite disease. Disease progression may or may not proceed in a manner that leads to the evolution of patients through all 3 categories. Indeed, a patient initially diagnosed as having possible ALS may progress to death without ever satisfying criteria for probable or definite disease. Traynor and colleagues (Traynor et al., 2000) found that patients initially diagnosed with possible ALS had a 22% chance of death from ALS even though their diagnostic category did not change.

A third concern arising from current criteria is that patients with upper motor neuron signs in 2 body regions are classified as having possible ALS, even without the presence of any lower motor neuron signs. Such patients may ultimately be diagnosed as having Primary Lateral Sclerosis based on progressive upper motor neuron dysfunction in the absence of lower motor neuron signs for at least 4 years after disease onset (Turner et al., 2020). These patients have a more protracted disease course and may never show the lower motor neuron decline that defines ALS.

Finally, in the years since the Awaji Criteria were published, there have been significant advances in neurophysiological probes of upper motor neuron dysfunction, as well as advances in imaging, genetics, and the development of fluid biomarkers (Turner, 2018; Rutkove et al., 2012; Turner et al., 2011). The presence of cognitive and behavioural change, now known to occur in up to 50% of those with ALS, and the association with Frontotemporal Dementia in 15% of patients, were not recognized in the original criteria (Strong et al., 2017).

For all of these reasons, a consensus conference sponsored by the International Federation of Clinical Neurophysiology, the World Federation of Neurology, the ALS Association, and the MND Association was convened September 27–29, 2019 at Gold Coast, Australia to evaluate whether new guidelines could simplify diagnosis and take into account new data that might be incorporated into the criteria for ALS. Attendees recognized that ALS can involve more than the motor system, and that cognitive, behavioural, and psychiatric disturbances can be part of the disease. The current state of knowledge of the genetics of ALS was reviewed, as were new modalities for assessing both peripheral motor and central disease. While further research on methods to assess both central and peripheral processes is required, recommendations for modification of the existing criteria focused on simplifying how the diagnosis can be established, and in establishing a single clinical diagnostic entity rather than different disease categories.

The following statements summarize our current understanding of ALS.

1. ALS is a progressive disorder of the motor system
   a. Clinically focal onset is most frequent, but a generalized symptom onset is also recognized.
   b. The motor disorder in ALS reflects both lower and upper motor neuron dysfunction, but it is recognized that upper motor neuron signs are not always clinically evident.
   c. Evidence of lower motor neuron dysfunction can be derived from clinical examination and/or from EMG.
   d. For the purpose of diagnosis, evidence of upper motor neuron dysfunction is currently derived from clinical examination.
   e. Supportive evidence of lower motor neuron dysfunction can be derived from ultrasound detection of fasciculations from multiple muscles (Tsugawa et al., 2018). Supportive evidence of upper motor neuron dysfunction can be derived from transcranial magnetic stimulation studies of the central motor nervous system, MRI, and neurofilament levels (Bowser et al., 2011). It should be stressed that current diagnosis does not require these studies.
2. ALS may include cognitive, behavioral and/or psychiatric abnormalities although these are not essential for diagnosis.

Our proposed diagnostic criteria are presented in Table 1. We hope that the simplicity of the criteria below will allow them to be used by both clinicians and in the clinical trial setting.

We note that these proposed criteria represent expert opinion and validation studies should be performed to establish their utility. It should be noted, however, that these criteria closely resemble those previously required using the Awaji revision of the revised El Escorial Criteria for the diagnosis of Possible ALS. Thus, criteria very similar to what we propose have previously been employed in clinical trials.

Several aspects of these simplified criteria merit discussion. First it should be stressed that cognitive and behavioural changes are common in ALS, and diagnostic criteria have already been established (Strong et al., 2017) to categorize these changes. These criteria should be included in current and future diagnostic classifications of ALS. Second, despite the advances in the genetics of ALS, the presence or absence of specific mutations currently plays no role in the above criteria. This decision was made because the presence of a risk factor does not in itself indicate the disease process is taking place, while on the other hand the simple criteria above are both necessary and sufficient. As gene therapies are developed, it may become appropriate to modify the criteria to allow specific gene variations to be taken into account. This will require consensus on which gene variations should carry diagnostic weight and will need to be reviewed periodically as new ALS gene variations are discovered. Third, while the available data at present do not support use of imaging or neurophysiological modalities to establish the presence of upper motor neuron dysfunction, it is anticipated that future studies will allow such data

Table 1
Criteria for diagnosis of ALS.

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and
2. Presence of upper[1] and lower[2] motor neuron dysfunction in at least 1 body region[3], (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least 2 body regions, and
3. Investigations[4] excluding other disease processes

Footnotes:

[1]Upper motor neuron dysfunction implies at least one of the following:
1. Increased deep tendon reflexes, including the presence of a reflex in a clinically weak and wasted muscle, or spread to adjacent muscles
2. Presence of pathological reflexes, including Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex.
3. Increase in velocity-dependent tone (spasticity)
4. Slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or Parkinsonian features

[2]Lower motor neuron dysfunction in a given muscle requires either:
Clinical examination evidence of
Muscle weakness, and
Muscle wasting
or
EMG abnormalities that must include:
Both evidence of chronic neurogenic change, defined by large motor unit potentials of increased duration and/or increased amplitude, with polyphasia and motor unit instability regarded as supportive but not obligatory evidence.
And evidence of ongoing denervation including
Fibrillation potentials or positive sharp waves, or
fasciculation potentials

[3]Body regions are defined as bulbar, cervical, thoracic and lumbosacral. To be classified as an involved region with respect to lower motor neuron involvement, there must be abnormalities in two limb muscles innervated by different roots and nerves, or one bulbar muscle, or one thoracic muscle either by clinical examination or by EMG.

[4]The appropriate investigations depend on the clinical presentation, and may include nerve conduction studies and needle EMG, MRI or other imaging, fluid studies of blood or CSF, or other modalities as clinically necessary.

to play a role in diagnosis. Fourth, while the presence of fasciculations is not required to make the diagnosis of ALS, we recognize that diffuse fasciculations renders the diagnosis more likely, and their absence should spur the clinician to consider other diagnoses as appropriate. Fifth, it is recognized that both fluid and imaging studies may ultimately allow for specific diagnosis, (for example, a probe for the presence of TDP43 pathology). However, these potential biomarkers remain at the experimental stage. Finally, we feel that abnormalities should be grouped in body regions for a diagnosis of ALS to be clear. Spotty abnormalities scattered throughout the neuraxis may have a broader differential diagnosis and be more prone to misdiagnosis than abnormalities occurring consistently in one or more regions of the body. For that reason, we have maintained the description of body regions in a manner similar to the revised El Escorial Criteria. We have also maintained the role of EMG/NCS in ALS diagnosis; in the opinion of the Consensus Group, this test is a critically important although not obligatory investigation aimed at eliminating other nerve diseases as possible etiologies of LMN dysfunction, and facilitating diagnosis by identifying muscles which clinically are not identified as showing evidence of LMN dysfunction.

To summarize, the criteria as presented represent the minimum necessary abnormalities to arrive at a diagnosis of ALS. The objective has been to simplify by collapsing the criteria for possible, probable, and definite disease into a single entity from a clinical management perspective. Enrolment into clinical trials should use these criteria for diagnostic purposes; we recognize that individual clinical trials are likely to have additional inclusion criteria which may further define the population to be studied within that trial.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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(*continued on next page*)

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