Clinical Neurophysiology 127 (2016) 2684–2691

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Awaji criteria improves the diagnostic sensitivity in amyotrophic lateral sclerosis: A systematic review using individual patient data

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See Editorial, pages 2682–2683

ARTICLE INFO

Article history:
Accepted 1 April 2016
Available online 16 April 2016

Keywords:
Awaji criteria
El Escorial criteria
Amyotrophic lateral sclerosis
Meta-analysis

HIGHLIGHTS

- Individual patient data analysis disclosed a higher sensitivity of the Awaji criteria when compared to the revised El Escorial criteria.
- Modification of Awaji criteria, to include a "possible" diagnostic category significantly enhanced the diagnosis of ALS, particularly in limb onset disease.
- Disease duration exerted a significant effect on the diagnostic utility of the Awaji criteria.

ABSTRACT

Objective: To determine the utility of the Awaji criteria in diagnosing amyotrophic lateral sclerosis (ALS) and to propose a novel modification so as to enhance sensitivity based on results of individual patient data (IPD).
Methods: Individual patient data were available from 8 studies comparing the diagnostic accuracy of Awaji and revised El Escorial (rEEC) criteria. The sensitivity of a novel updated Awaji criteria, incorporating a "probable-laboratory supported" category, was also tested.
Results: Individual patient data were available from 1086 patients, consisting of 881 ALS and 205 patients with disorders mimicking ALS. Summary sensitivities based on random effects logistic regression modelling disclosed a higher sensitivity of the Awaji criteria (0.70, 95% confidence interval [CI] 0.51–0.83) and updated Awaji criteria (0.73, 95% CI 0.56–0.85) when compared to rEEC (0.58, 95% CI 0.48–0.68). Paired analysis revealed higher sensitivities of Awaji criteria in 4 studies, and of updated Awaji criteria in 7 studies, when compared to rEEC.
Conclusion: Individual patient data analysis established a higher sensitivity of Awaji criteria when compared to rEEC. The updated Awaji criteria enhanced the diagnostic sensitivity in limb-onset ALS.
Significance: The updated Awaji criteria should be considered in clinical practice and future therapeutic trials.

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http://dx.doi.org/10.1016/j.clinph.2016.04.005
1388-2457/

1. Introduction

There is no diagnostic test for amyotrophic lateral sclerosis (ALS), a rapidly progressive and fatal neurodegenerative disorder of the motor neurons (Kiernan et al., 2011). Rather, diagnosis of ALS relies on the identification of a combination of upper (UMN) and lower motor neuron (LMN) clinical signs across specific body regions (Brooks et al., 2000; de Carvalho et al., 2008; Kiernan et al., 2011). Clinically based diagnostic criteria (El-Escorial and Airlie House, also known as revised El-Escorial) were designed to be highly specific for ALS, although their sensitivity is limited, particularly in early stages of the disease (Aggarwal and Cudkowicz, 2008; Chio, 1999; Turner et al., 2009). Consequently, significant diagnostic delays are inevitable, leading to delay in the institution of neuroprotective therapies and recruitment into therapeutic trials, perhaps beyond the therapeutic window period.

The neurophysiologically based Awaji criteria were developed (de Carvalho et al., 2008) for use in conjunction with the clinical criteria as set out in the revised El-Escorial criteria (rEEC), in an attempt to reduce diagnostic delays. The Awaji criteria proposed that neurophysiological features of LMN dysfunction, including chronic and ongoing neurogenic changes (fibrillation potentials/-positive sharp waves) were equivalent to clinical LMN signs. In addition, fasciculations were deemed to be a biomarker of LMN dysfunction when combined with chronic neurogenic changes. Subsequently, the diagnostic utility of the Awaji criteria was assessed in retrospective and prospective studies, which established an increased or comparable sensitivity when compared to rEEC (Boekestein et al., 2010; Chen et al., 2010; Costa et al., 2012; de Carvalho and Swash, 2009; Douglass et al., 2010; Gawel et al., 2014; Krarup, 2011; Okita et al., 2011; Schrooten et al., 2011), although one study reported a lower sensitivity, a finding attributed to the omission of a "probable-laboratory supported" diagnostic category (Higashihara et al., 2012).

The diagnostic accuracy of the Awaji criteria was also assessed in two study-level meta-analyses, and these reported an improved diagnostic performance of the Awaji criteria, with higher sensitivity and diagnostic odds ratios (Costa et al., 2012; Jang and Bae, 2015). The diagnostic benefits, however, appeared to be most prominent in ALS patients with bulbar-onset disease. Interestingly, one study reported that 20% of patients classified as "probable laboratory-supported" on the rEEC were downgraded to Awaji "possible" (Jang and Bae, 2015), although this latter study was criticised for utilising incomplete data sets (de Carvalho et al., 2015). Importantly, both study-level meta-analyses were limited by high heterogeneity of pooled sensitivity estimates, potentially impacting on outcomes.

In order to maximise the statistical power of the analysis, and explore variation at an individual patient level, we aimed to perform a systematic review using individual patient data. In particular, we aimed to (1) summarise diagnostic accuracy of the rEEC, Awaji and the updated Awaji criteria (an extension of the Awaji criteria whereby lower motor neuron dysfunction in two regions along with UMN signs in one region were regarded as diagnostic of ALS), (2) explore reasons for heterogeneity in diagnostic accuracy for each criterion using patient and study level covariates, (3) compare diagnostic accuracy of the rEEC versus the Awaji and updated Awaji criteria, and (4) explore differences in accuracy for the diagnostic criteria, when applied to the bulbar and limb-onset subgroups.

2. Methods

2.1. Selection and eligibility criteria

All studies assessing the diagnostic accuracy of rEEC and the Awaji criteria in ALS were considered eligible for analysis. Studies were included regardless of the electromyography (EMG) protocol utilized in patient evaluation, although a minimum of 2 muscles needed to be assessed in the cervical (upper limbs) and lumbosacral (lower limbs) regions and one muscle in bulbar and thoracic paraspinal regions. The accepted diagnosis of ALS was defined by good clinical practice as described in the studies, requiring disease progression deemed to be consistent with ALS and clinical progression was used as the reference (gold) standard. In addition, exclusion of potential mimic disorders by clinical, neuro-

Table 1
Summary of the revised El Escorial criteria (rEEC), Awaji criteria and updated Awaji criteria. The neurophysiological definition of lower motor neuron (LMN) dysfunction for the rEEC includes; (i) presence of fibrillation potentials and positive sharp waves; (ii) evidence of reinnervation (large amplitude, long duration polyphasic motor unit action potentials); and (iii) reduced interference on full contraction with increased firing rate of motor units on voluntary contraction. The definition of LMN dysfunction using the Awaji and updated Awaji criteria is as follows: (i) presence of fibrillation potentials and positive sharp waves or fasciculation potentials; (ii) evidence of reinnervation (large amplitude, long duration polyphasic motor unit action potentials); and (iii) reduced interference on full contraction with increased firing motor unit rate upon voluntary contraction. In order for a region to be classified as affected the neurophysiological changes have to be evident in a minimum of 2 muscles innervated by different nerve roots and nerves for spinal and lumbosacral regions; and a minimum of one muscle in the bulbar/thoracic regions. The assessment of upper motor neuron dysfunction remains clinically based.

Diagnostic ALS category	Revised El Escorial criteria (Airlie House 1998)	Awaji criteria	Updated Awaji criteria
Definite	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in the bulbar region and at least 2 spinal regions, or 3 spinal regions	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in the bulbar region and at least 2 spinal regions, or 3 spinal regions	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in the bulbar region and at least 2 spinal regions, or 3 spinal regions
Probable	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in at least 2 regions with some upper motor neuron signs necessarily rostral (above) to lower motor neuron dysfunction	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in at least 2 regions with some upper motor neuron signs necessarily rostral (above) to lower motor neuron dysfunction	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in at least 2 regions with some upper motor neuron signs necessarily rostral (above) to lower motor neuron dysfunction
Probable-laboratory supported	Clinical signs of upper and lower motor neuron dysfunction in one region together with neurophysiological evidence of lower motor neuron dysfunction in 2 regions	Omitted	Clinical signs of upper and lower motor neuron dysfunction in one region together with neurophysiological evidence of lower motor neuron dysfunction in 2 regions
Possible	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in one region, or Upper motor neuron signs evident in 2 regions, or lower motor neuron dysfunction evident rostral (above) to upper motor neuron signs	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in one region, or Upper motor neuron signs evident in 2 regions, or lower motor neuron dysfunction evident rostral (above) to upper motor neuron signs	Clinical or neurophysiological evidence of upper and lower motor neuron dysfunction in one region, or Upper motor neuron signs evident in 2 regions, or lower motor neuron dysfunction evident rostral (above) to upper motor neuron signs