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REVIEW ARTICLE

Accelerate the diagnosis of amyotrophic lateral sclerosis using the Gold Coast criteria and biomarkers

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Abstract

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disorder characterized by upper and lower motor neurons death, the diagnosis remains in clinical basis. Clinical criteria El Escorial for its diagnosis were published in 1994, the revised criteria in 2000 and modified by the Awaji criteria in 2008 to integrate electrophysiological data with the clinical examination. These criteria are complex to apply and have difficulties to determine progression through ALS categories. Recent advances in genetics, biomarkers such as light chain neurofilament (NfL), cytokines, neuroimaging, and neurophysiological probes of upper motor neuron dysfunction are not included in the diagnostic criteria. In 2019, new and simple ALS diagnostic criteria (Gold Coast criteria) have been introduced along with genetic testing and serum and cerebrospinal fluid NfL levels. Early diagnosis for initiating disease-modifying drugs and care in a multidisciplinary ALS clinic will improve quality of life and survival in ALS patients. In this article, I consider that it is an urgency to facilitate an early recognition of possible ALS among primary care physicians as well as to foster of urgency among neurologist to accelerate the diagnostic process of ALS to protect viable motor neurons and slow down the process of neurodegeneration.

Keywords: *Amyotrophic lateral sclerosis. Gold Coast criteria. Biomarkers. Riluzole. Edaravone. Relyvrio.*

Acelerar el diagnostico de esclerosis lateral amiotrófica utilizando los criterios Gold Coast y biomarcadores

Resumen

La esclerosis lateral amiotrófica (ELA) es un trastorno neurodegenerativo crónico caracterizado por la muerte selectiva de las neuronas motoras superiores (NMS) y neuronas motoras inferiores. El diagnóstico permanece en bases clínicas. Los criterios clínicos de El Escorial descritos en 1994, fueron revisados el año 2000 y modificados por criterios de Awaji en 2008 integrando datos clínicos y electrofisiológicos. Estos criterios son complejos para aplicarse, propensos a errores y difíciles de determinar evolución. Avances recientes en genética, biomarcadores como neurofilamento de cadena ligera (NfL), citocinas, neuroimagen y estudios neurofisiológicos no se incluyen en los criterios de diagnóstico actuales. En 2019, se introdujeron criterios nuevos y simples para el diagnóstico de ALS (criterios de Gold Coast) que incluyen imagen de resonancia magnética, biomarcadores en sangre y líquido cefalorraquídeo (NfL) y pruebas genéticas. El diagnóstico temprano para iniciar fármacos modificadores de la enfermedad y la atención en clínicas multidisciplinarias para ELA mejorarán calidad de vida y sobrevida de los pacientes. En este artículo, considero urgente facilitar el

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reconocimiento temprano de una posible ELA entre los médicos de atención primaria y neurólogos para acelerar el proceso diagnóstico de la ELA y tratar de proteger las neuronas motoras viables y desacelerar el proceso de neurodegeneración.

Palabras clave: *Esclerosis lateral amiotrofica. Biomarcadores. Riluzole. Edavarona. Relyvrio.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal, chronic progressive neurodegenerative disorder characterized by progressive death of cortical upper motor neurons (UMN) and lower motor neurons (LMN) at the bulbar and spinal cord level[1]. It is well recognized that the disease of ALS starts long before symptom onset, a human autopsy study indicated that ~ 20% loss of motor neurons had already occurred in anterior roots in the presymptomatic stage[2]. A significant loss of neurons before the clinical onset has also been described in Parkinson´s disease, another neurodegenerative disorder[3]. ALS is characterized by progressive loss of function of the muscles in the limbs and those needed for speech, swallowing, and breathing. Most of these patients die due to respiratory failure around 3 years after clinical onset.

Clinical observations demonstrate that there is a considerable variation in the phenotypic expression of ALS, the variability goes far beyond the site of onset, also including, age of beginning, familial occurrence, type and degree of UMN or LMN involvement and extent of extramotor contribution[1]. Since the first description by Jean-Martin Charcot in 1874, the diagnosis is based in clinical features[4]. ALS is the most common adult motor neuron disease with an estimated incidence of two per 100,000 persons and estimated prevalence of five cases per 100,000 persons. The mean age at onset in hispanic ALS patients was reported to be 47.5 ± 10.5 years, the age at onset was earlier than in the Caucasian series[5]. Familial ALS accounts for 10-15% of cases, and the remaining ALS cases, 85-90% are sporadic with undefined etiology[6,7]. So far, more than 50 causative or disease modifying genes have been identified and the genetic analysis, can consider gene mutations associated to ALS[6].

ALS diagnosis

No definitive diagnostic test for ALS has been developed, originally the diagnostic criteria were established because the variety of clinical features early in the course of ALS compromises the certainty of diagnosis for clinical research and therapeutic trials. The El Escorial criteria were created and initially published in 1994 to stratify patients and facilitate ALS research. These criteria described four categories of disease: Definite, Probable, Possible, and Suspected ALS. El Escorial revised criteria in 2000, included a category called “laboratory supported probable ALS” that allowed the use of electromyography data, and the category of suspected ALS was deleted[8].

The Awaji criteria announced in 2008, modified the El Escorial revised criteria to further integrate electrophysiological data with clinical examination findings, and to add the presence of fasciculations as a lower motor neuron sign. The Awaji criteria maintained the definite, probable, and possible categories. The revised El Escorial and the Awaji criteria are difficult to apply in patients being evaluated for ALS scoring low for both criteria, as well as the reliability for neurophysiologists of variable experience. These categories indicate how many body regions are affected by ALS, however, are often unrecognized by patients and clinicians as a probability of ALS[9]. El Escorial and the Awaji criteria have limitations including complexity to apply, prone to error, difficulties to determine when a possible ALS evolves through other ALS categories and does not ascertain type, site, and extension of the clinical signs of UMN dysfunction. Moreover, neurophysiological and neuroimaging probes of UMN dysfunction are not included[9].

Biomarkers

Since the publication of the Awaji criteria, significant advances have been made in the genetics of ALS, fluid biomarkers including neurofilament light chain (NfL), phosphorylated neurofilament heavy chain (pNfH)[2], a number of cytokines, neuroimaging tractography by means of magnetic resonance imaging (MRI) including diffusion tensor imaging (DTI) of the pyramidal tract with fractional anisotropy (FA), and neurophysiological probes of UMN dysfunction by means of transcranial magnetic stimulation, these biomarkers have been reported in the literature[10-12]. Recent reports, describe that NfL serum levels are considered useful for an early diagnosis of ALS[2]. Current diagnosis criteria do not include none of these biomarkers in the diagnosis of ALS or in establishing the abnormal function of the UMN[9-12].

A consensus conference organized in Gold Coast Australia and sponsored by the World Federation of Neurology evaluated whether new guidelines could simplify the diagnosis and a proposal for new diagnostic criteria for ALS was published[9]. In 2019, the Gold Coast criteria were developed with the aim of simplifying diagnosis of ALS with a single clinical diagnostic entity while taking new data into account, particularly involvement of more than the motor system and cognitive, behavioral, and psychiatric disturbances. The new criteria are simple and capture disease characteristics that are necessary and sufficient for diagnosis of ALS. The old revised El Escorial and Awaji criteria only intended for stratifying patients for clinical trials, the new Gold Coast criteria can be used in both clinical setting and clinical trials.

Advances in the genetics of ALS, fluid biomarkers, neuroimaging, and neurophysiological modalities will play a role in the early diagnosis of ALS[7,10,12]. While the available data at the present does not support the use of biomarkers serum levels, the NfL and pNfH are considered as the most promising biomarkers for an early diagnosis of ALS[2,9]. Several neuroimaging reports have described a different MRI signs in ALS patients including: I. The bright-tongue sign[13], (Fig. 1A and B), this sign does not constitute a reliable diagnostic criterion for ALS and usually appears late in bulbar and bulbospinal ALS; II. The motor-band sign is an hypointense signal in the precentral gyrus in MRI susceptibility-weighted images that it is not frequently observed and also usually exists in advanced illness[14]; III. The corticospinal hyperintensity signal, it is not a useful marker to define progression of the illness and appears late in some ALS patients (Fig. 2). In the other hand, the FA of the pyramidal tract derived from MRI-DTI is an informative measure of axonal fiber degeneration and myelin breakdown and this neuroimaging method may be useful to confirm UMN impairment in ALS patients as well as to determine effectiveness of therapies in clinical trials (Fig. 3)[15]. The split-hand phenomenon, the bright tongue sign, the motor-band sign and the corticospinal hyperintense signal are not supported as possible early biomarkers in ALS and they are usually observed when the ALS patients are in advanced clinical stage.

The new Gold Coast diagnostic criteria

To diagnose ALS using Gold Coast criteria the patient must have: (1) progressive motor impairment of history of repeated clinical evaluation, preceded by normal motor function; (2) presence of both UMN and LMN abnormalities in at least one body region (with UMN and LMN noted in the same body region if only 1 region is affected) or LMN abnormalities in two body regions; and (3) excluding other disease processes (Table 1). The Gold Coast criteria have been introduced along with genetic testing and serum and cerebrospinal fluid NfL levels to establish an early diagnosis of ALS. Then an early initiation of care in multidisciplinary clinics as well as starting disease-modifying drugs (riluzole, edaravone, and sodium phenylbutyrate-taurursodiol) will improve quality of life and survival in ALS patients. It is crucial to accelerate the diagnostic process of ALS among neurologists to protect viable motor neurons and slow down the process of neurodegeneration.

With the growing of multidisciplinary care clinics around the world including in our country[16], ALS patients are submitted to a thorough clinical evaluation

Table 1. Summary of The Gold Coast criteria[9]

– Documented history or repeated clinical assessment indicating progressive motor impairment, preceded by normal motor function
– Presence of UMN* and LMN† dysfunction in at least one body region (bulbar, cervical, thoracic, and lumbosacral), with UMN and LMN dysfunction noted in the same body region if only one body region is involved, or LMN dysfunction in at least two body regions. The abnormalities must be in two limbs muscles innervated by different roots and nerves, or one bulbar muscle, or one thoracic muscle either by clinical examination or by electromyography
– Investigations that exclude other diseases processes, depending upon clinical presentation, and may include nerve conduction studies and Needle EMG, magnetic resonance imaging or other imaging, fluid studies of blood or cerebrospinal fluid, or other modalities as clinical necessary
UMN dysfunction defined by at least one of the following: – Increase deep tendon reflexes, including the presence of a reflex in a clinical weak and wasted muscle, or spread to adjacent muscles – Presence of pathological reflexes, including Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex – Increase in velocity-dependent tone (spasticity) – Slowed, poorly coordinated voluntary movement that is not attributable to weakness of LMN origin or Parkinsonian features
LMN dysfunction in a given muscle defined as one of the following – Clinical examination evidence of muscle weakness and muscle wasting – EMG‡ abnormalities that must include: – Evidence of chronic neurogenic change (large motor unit potentials of increased duration). Polyphasia and motor unit instability are regarded as supportive but not requisite evidence – Evidence of ongoing denervation including fibrillation potentials or positive sharp waves, or fasciculation potentials

*UMN: upper motor neuron;
†LMN: lower motor neuron;
‡EMG: electromyography.

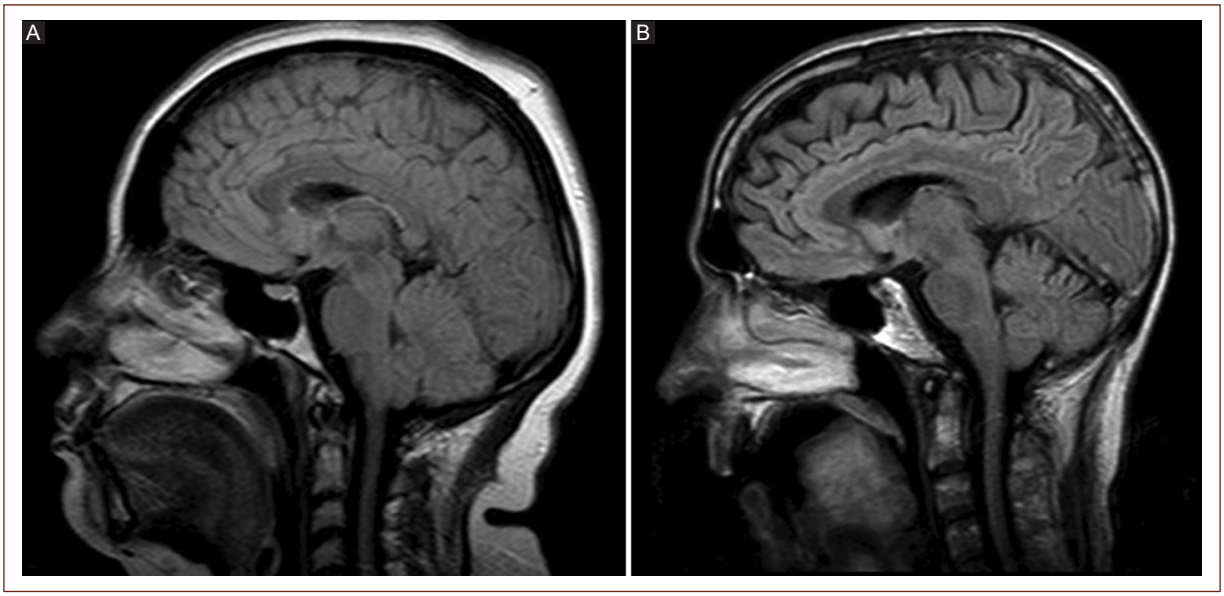

Figure 1. Bright tongue sign. Magnetic resonance imaging (MRI) sagittal T1-weighted FLAIR sequence **A:** in a 41-year-old female with 6 months from onset to diagnosis of bulbospinal amyotrophic lateral sclerosis (ALS). Shape and signal intensity of her tongue were normal, **B:** MRI in a 49-year-old man with 23 months from onset to diagnosis of bulbospinal ALS. Abnormalities in shape, position, and hyperintense signal of the tongue were detected.

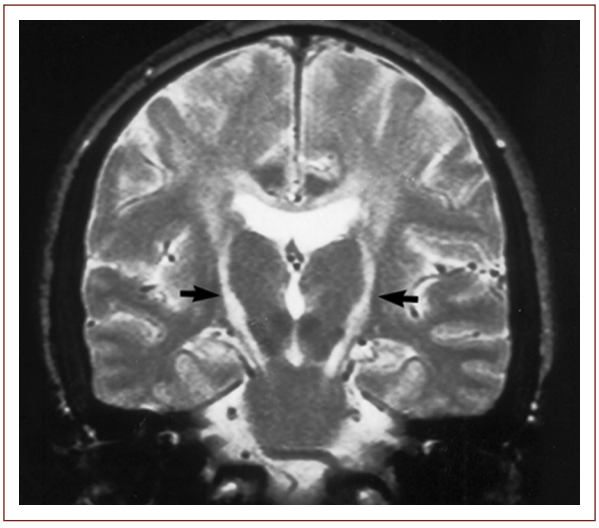

Figure 2. Magnetic resonance imaging coronal T2-weighted sequence showed high intensity signal in the pyramidal tract (arrows). The hyperintense signal started in frontal motor cortices.

identifying abnormalities that are managed appropriately. Early enrollment of patients with ALS into multidisciplinary clinics was associated with early initiation of non-invasive ventilator, clearly leading to an extension of survival and significant cost savings, which can be substantial[2,16,17]. Moreover with the advances in clinical trials ALS has become a treatable (but not curable) disease[6]. Three medications have been approved by the U.S. Food and Drug Administration (FDA) riluzole (in 1995), edaravone (in 2017), and sodium phenylbutyrate-taurursodiol (2022)[7,18-20].

Results of Clinical Trials

Riluzole (Rilutek®)

A 2-aminobenzothiazide, until the last decade was the only disease-modifying therapy available for ALS[18,21,22]. Although it is known that this medication modulates excitatory neurotransmission, the precise neuroprotective mechanisms remain largely speculative. A study based on the analyses from a large PRO-ACT data base revealed that early initiation of riluzole led to survival benefits. The greatest benefits occurred when this medication was initiated during the first 18-24 months after diagnosis[2,18,23].

Edaravone (Radicava®)

A potent pyrazalone free radical scavenger provided as a sterile injection solution for IV infusion containing 30 mg in 100 mL isotonic solution[19]. The mechanism of action in ALS may be due to its known antioxidant

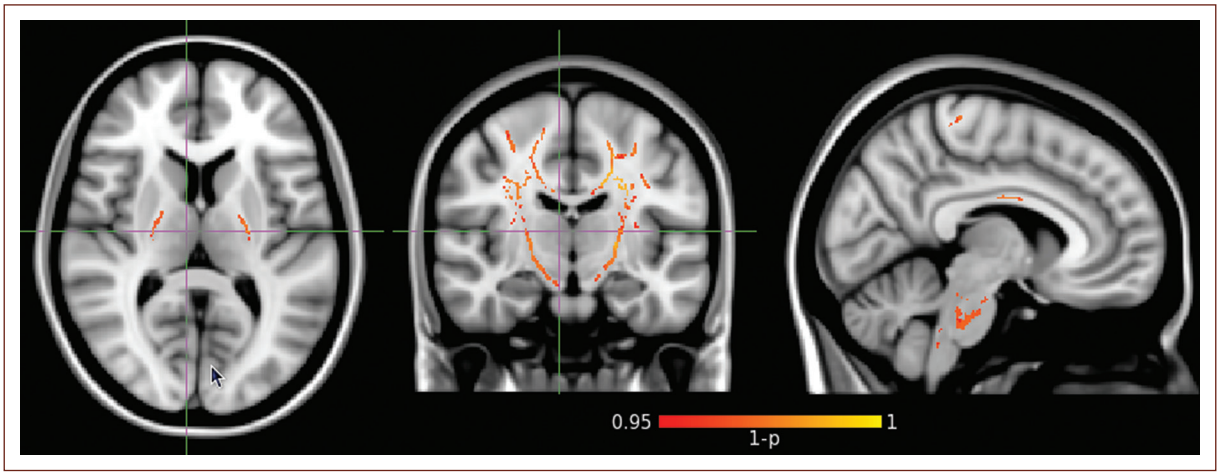

Figure 3. Magnetic resonance imaging-diffusion tensor imaging based analysis in 11 amyotrophic lateral sclerosis (ALS) subjects versus eight control subjects. FA maps on all brain white matter. FA is smaller (orange) in ALS subjects when compared with controls ($p < 0.05$, corrected). Axial, coronal, and sagittal views.

properties since oxidative stress is a part of the process that kills neurons in ALS patients. A 6-month, randomized, placebo-controlled, double-blind study conducted in Japanese patients with ALS demonstrated the efficacy of edaravone for the treatment of ALS. The decline in ALSFRS-R scores from baseline was significantly less in the edaravone group (–5.01 ± 0.64) compared with the placebo group (–7.50 ± 0.66) ($p = 0.0013$)[19,24,25]. In May 2022 the FDA approved edaravone oral suspension for the treatment of adults with ALS.

Sodium Phenylbutyrate-Taurursodiol (Relyvrio™)

This recently approved medication is a coformulation of sodium phenylbutyrate and taurursodiol[20]. It was designed to mitigate the effects of accumulation of misfolded proteins and promote neuron survival[26]. The neuroprotective effect of this medication, minimizes cell death triggered through oxidative stress by blocking apoptotic responses[27]. The recent placebo-controlled phase 2 CENTAUR trial, sodium phenylbutyrate-taurursodiol treatment group showed statistically significant slowing in functional decline over 24 weeks according to the ALSFRS-R by 24 weeks (–1.24 points per month with sodium phenylbutyrate-taurursodiol vs. –1.66 points per month with placebo; difference, 0.42 points per month; 95% CI: 0.03-0.81; $p = 0.03$). When all participants who had completed the 24-week placebo-controlled phase, they were invited to be enrolled in an open-label extension of the trial and treated with sodium phenylbutyrate-taurursodiol[28]. ALS patients who had originally been randomized to sodium phenylbutyrate-taurursodiol experienced a 44% reduction in the risk of death and a median 6.5-month increase in overall survival relative to those who had received placebo ($p = 0.023$), highlighting the importance of early ALS diagnosis and initiation of disease-modifying treatment[26]. This medication was FDA approved on September 2022. Additional investigational drugs are being evaluated for their abilities to prolong survival and slow disease progression.

Discussion

In ALS, the loss of neurons occurs long before symptom onset and neuronal death have occurred in the anterior roots in the presymptomatic stage[1]. The diagnostic delay remains unchanged at least during the past two decades[2]. The delay is due to a several reasons including (a) variable phenotypic expression of ALS[1]; (b) deprived knowledge of general physicians to recognize characteristic features of ALS[2]; (c) El Escorial and the Awaji criteria are complex to apply, prone to error and with difficulties to ascertain changes through the categories to diagnose definite ALS[9]; and (d) neurologist question the need to hasten a diagnosis of ALS since no definitive diagnostic test has been developed and ALS remains as an incurable disease[2]. However, there are some important changes in the management of ALS patients: (1) early enrollment of patients with ALS into multidisciplinary clinics are associated with clearly leading to an extension of survival, quality of life and significant cost savings[14,15]; (2) the new developed Gold Coast criteria were developed to simplify and hastening

ALS diagnosis[9]; and (3) riluzole[18], edaravone[19], and sodium phenylbutyrate-taurursodiol[20] approved by the FDA, have shown improvement in survival, quality of life, as well as in the score of the ALSFRS-R and Forced Vital Capacity (FVC), highlighting the importance of an early diagnosis of ALS and prompt initiation of disease-modifying treatment[18-28].

Conclusion

At the present time, it is considered the advantage of using the Gold Coast criteria to confirm ALS diagnosis at an early stage of the disease. ALS diagnosis without delay is essential for initiating disease-modifying treatment and care in a multidisciplinary ALS clinic that will improve quality of life and survival in ALS patients. It is a necessity to enable an early recognition of possible ALS among primary care physicians as well as to foster among neurologists to accelerate the diagnostic process of ALS to protect viable motor neurons and slow down the process of neurodegeneration.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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