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Classification of amyotrophic lateral sclerosis cases at presentation in epidemiological studies

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Abstract Amyotrophic lateral sclerosis (ALS) diagnosis is based exclusively on clinical grounds because of the absence of biological markers and of specific neuroradiological and neurophysiological diagnostic features. A clinical classification system of cases has been introduced (El Escorial Criteria, EEC) and then revised after the inclusion of the neurophysiologic assessment (Airlie House Criteria, AHC) for enrolment of patients in clinical trials. The aim of this study is to present cases at presentation in the early stages of the disease that have difficult allocation both in EEC and AHC. All cases were subjects enrolled through SLAP, a population-based registry based in Puglia, Southern Italy. Although differential diagnosis excluded ALS-mimic syndromes, we identified four cases (out of 130 cases, 3.1%) that did not meet the EEC and AHC at the first visit. Even though the number of unclassifiable

cases is small, both EEC and AHC may be restrictive. This precludes the enrolment of ALS cases at an early stage both in observational studies and clinical trials.

Key words Amyotrophic lateral sclerosis • El Escorial criteria • Suspect ALS

Introduction

The diagnosis of amyotrophic lateral sclerosis (ALS) is based on clinical grounds because of the absence of a biological marker and of specific neuroradiological or neurophysiologic diagnostic features. One set of criteria, based on clinical grounds (El Escorial Criteria, EEC) [1] was introduced for the enrolment of patients in clinical trials. EEC was recently revised after the addition of neurophysiological features to clinical criteria (Airlie House criteria, AHC) [2]. The goal of the new criteria was to classify earlier the patients in the categories of high diagnostic certainty (definite and probable-ALS). Both EEC and AHC have been widely used in clinical trials but also in clinical and observational epidemiologic studies.

The aim of this study is to present cases recruited from a population-based registry that could not be classified according to EEC and AHC at their first visit.

Source of cases and case description

The source of cases for this study is Sclerosi Laterale Amiotrofica – Puglia (SLAP), an ongoing multicentre prospective registry of ALS incident cases. In the two-year period 1998–99 we identified 130 cases, four of which were not classifiable, using the EEC and AHC [3].

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Case 1

A 65-year-old man presented with a 3.3-year progressive history of weakness and atrophy of both upper limbs. Neurological examination revealed diminished power (4/5 using the MRC Scale), atrophy and fasciculations in both upper limbs, associated with diminished deep tendon reflexes. Lower limb examination, coordination and all sensory modalities were preserved. Magnetic resonance images (MRI) of the brain and spinal cord were normal. Electromyography (EMG) showed chronic neurogenic features with fibrillations and fasciculations in muscles of all four limbs. Nerve conduction velocities were normal. In the next few months lower limbs were involved and after one year upper motor neuron signs (UMN) were also present in the four limbs.

Comment: this case at the first visit was a LMN syndrome (LMNS) in one region.

Case 2

A 52-year-old woman had some difficulties in speaking and in swallowing with progressive course for the previous 6 months. Dysarthria, dysphagia with tongue atrophy and fasciculations were present. Strength, tone and deep tendon reflexes were normal in the four limbs. Laboratory examinations were unremarkable. EMG of muscles of the four limbs and MRI of the brain and spinal cord were normal.

Within six months the patient developed UMN bulbar signs (gag reflex and forced yawning). After ten months she developed both UMN and LMN signs in the four limbs.

Comment: we initially identified only LMN signs in the bulbar region.

Case 3

A 66-year-old woman developed in the previous 7 months progressive weakness and atrophy first in the right leg, then in the left leg. Neurological examination revealed weakness (4/5 using MRC), atrophy and fasciculations in both lower limbs. Deep tendon reflexes were hyperactive only in the right leg. Babinski sign was absent. Coordination and all sensory modalities were preserved. EMG revealed neurogenic change and fibrillations in lower limbs. Conduction studies, brain and spinal MRI were normal. The clinical features of the patient rapidly worsened and the patient died 10 months after the diagnosis.

Comment: the patient presented signs in only one region at the first visit.

Case 4

A 66-year-old man developed difficulties in speaking, progressively worsening in the previous 3.5 years. He presented dysarthria, tongue atrophy and fasciculations. Strength and tone were normal in muscles of all four limbs. Deep tendon reflexes were hyperactive in the upper limbs. Coordination and sensory modalities were preserved. Blood tests were normal. EMG showed a pattern of chronic denervation with fasciculations in facial muscles and chronic neurogenic changes without fibrillation in muscles of the four limbs. Conduction velocities and motor evoked potentials were normal. Brain MRI T2-weighted images showed hypointensity in right insular region, periventricular and subcortical white-matter hyperintensities. The clinical course of the patient was slowly progressive, with involvement in the following two years of both upper and lower limbs.

Comments: the hyper-reflexia of the upper limbs was attributed to subcortical vascular damage and he was classified as progressive bulbar palsy (PBP) presenting LMN signs in the bulbar region.

Discussion

In this study we have identified several sources of uncertainties in the classification of ALS cases at presentation using both EEC and AHC. All four cases reported here were not classifiable, although differential diagnosis excluded other ALS-mimic syndromes (like multifocal motor neuropathy and cervical spondylitic myelopathy). Cases 1 and 3 could not be classified because at the first clinical examination they did not satisfy the criteria of spread of signs in at least two regions. Cases 2 and 4 were difficult to classify because it was difficult to distinguish UMN and LMN signs in the bulbar region. In case 4 also the underlying lesion responsible for the UMN signs was not clear.

We found three sets of problems for the classification of ALS cases at presentation:

1. *Lack of spread of symptoms.* MND with focal presentation, like PBP and LMNS, may not be included in both EEC and AHC, because they may be characterised by the presence of LMN signs in only one region. The EEC requires the presence of LMN signs in at least two regions, while AHC does not include LMNS cases. It is unclear if PBP and LMNS are independent clinical entities or they represent clinical variants of ALS, even though several evidences support the second hypothesis. Commonly, the earliest clinical manifestations of ALS are focal or with predominant LMN involvement [4, 5]. In addition, autopsy and neurophysiological diagnostic studies demonstrated that the pyramidal tracts are often affect-

ed in patients with LMNS [6]. In subjects with only LMN presentation the ascertainment of UMN involvement could be improved with additional techniques, like proton magnetic resonance spectroscopy (PMRS) or transcranial magnetic stimulation.

Another problem in the search for spread of signs is that the thoracic region generally adds no further evidence to the neurological examination. LMN signs in this region, like weakness and atrophy of thoracic and abdominal muscles, are difficult to define, especially among elderly people. In addition, EMG of paraspinal muscles shows technical difficulties and is rarely done, even though it should be a standard component of ALS work-up [7]. Because of these problems, the search for spread of signs is generally made on only three regions (bulbar and limbs) and rarely on four.

2. *The distinction of UMN and LMN signs in the bulbar region.* UMN signs in the bulbar region, like clonic jaw, gag reflex and exaggerated snout reflex are difficult to elicit and commonly absent, especially in the earliest stage of the disease. In addition, signs like forced yawn are reported by the patient and rarely seen by the neurologist during the examination.

A clinical-pathological study revealed that UMN in the bulbar region are present in 20% of ALS patients at the onset and in 60% of the cases during the entire course of the disease [8]. Finally, in ALS patients bulbar signs such as dysarthria and dysphagia are present in a mixed form, with characteristics of both supranuclear and nuclear involvement.

A possible approach would be to include cases with bulbar onset within the category of possible ALS even when a clear distinction between UMN and LMN signs is not obtainable, especially if bulbar atrophy or EMG denervation are bilateral.

3. *Lack of specificity of UMN signs: neurodegeneration or vascular disease?* Attribution of UMN signs to ALS or to other neurodegenerative diseases like dementia or to vascular brain lesions is particularly difficult. Paraclinical exams do not seem to improve the specificity of UMN, although they may increase sensitivity in detection of UMN signs. MRI abnormalities have been found in less than one half of ALS patients and can be observed in healthy subjects as well as in other neurodegenerative diseases [9]. In addition, there is no consensus on which is the best spectroscopic marker of ALS [10]. Therefore, the attribution of UMN signs to ALS-related neurodegeneration of the corticospinal tract has to be based on the clinical judgement of the neurologist and on the clinical course.

Our case series originated from a population-based registry. Population series compared to clinical series from tertiary centres are better suited to be representative of the whole spectrum of the disease. This series suggests that 3% of the cases at presentation are not classifiable according to EEC and AHC. Even though the number of

unclassifiable cases is small, we have to consider that this comes about after an extensive clinical and instrumental investigation led by a neurologist. In a report from a population-based registry in Ireland the use of AHC did not succeed in the aim of shortening the time to trial eligibility, as 10% of the patients died without reaching the degree of defined or probable ALS and becoming trial eligible [11]. Based on these observations, EEC and AHC show a lack of sensitivity in the earliest stage of the disease. This may preclude the enrolment of ALS cases at an early stage both in observational studies and clinical trials.

The inclusion of cases at an earlier stage of the disease, at least in observational studies, could be possible if the following changes of the classifications would be made:

MND with bilateral LMN signs in one region or LMN signs in more regions should be classified as suspected ALS. The category suspected ALS as in EEC should be retained at least for epidemiological and natural history studies. This is in agreement with the recommendation of the European ALS consortium of population-based registries (EURALS) steering committee for inclusion criteria and diagnosis in ALS observational studies [12].

PBP presenting with dysarthria and dysphagia should be included as "possible ALS" even if there is no clear evidence of UMN bulbar signs.

The main component to the ALS diagnosis is progression. The definition of a specific time necessary to assess progression is however critical to reach homogeneity in the recruitment process both in observational and intervention studies. There is always a trade off between recruitment of true incident cases and diagnostic certainty. This is a problem common to all neurodegenerative diseases but could be especially critical for ALS where the optimal time useful for diagnostic, therapeutic decision and possible entry in clinical trials is relatively short.

We suggest that in cases in which an appropriate diagnostic investigation excluded ALS-mimic syndrome a minimum follow-up period should be defined to evaluate progression of signs, even if within only one region. In the vast majority of ALS cases a period between 6 and 12 months should be sufficient to make a judgement about progression. This would be consistent with previous suggestions based on the ALS Care Data set [6]. Misclassification of cases could represent a problem because the reliability of EEC is not optimal [13]. Thus, even though the number of false positive ALS might slightly increase, we could identify all the possible candidate ALS cases and study the whole clinical spectrum at every stage of the natural history of the disease. The utilisation of diagnostic criteria for clinical/epidemiological purposes should not be confused with their use for inclusion of subjects in clinical trials. At the same time the opportunity of trial inclusions for all ALS patients, including milder cases at earlier stage of disease, should not be overlooked. Further pathological studies on accuracy of

ALS diagnostic criteria should be conducted on large numbers of patients to assess the sensitivity and specificity of EEC and AHC and of modified less restrictive criteria.

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