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. 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 neurophysiological 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 neurophysiologic 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].
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 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.

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-