

SHORT COMMUNICATION

Signs and symptoms at diagnosis of amyotrophic lateral sclerosis: a population-based study in southern Italy

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Amyotrophic lateral sclerosis (ALS) diagnostic criteria are used to select patients for clinical trials based on different levels of diagnostic certainty, according to the spread of upper (UMN) and lower motoneuron (LMN) signs in different anatomic regions. However, the clinical presentation of ALS patients is extremely variable and this can delay the time to diagnosis and decrease the likelihood for trial entry. The aims of the study were to describe the signs and symptoms of diagnosis in a population-based incident cohort of ALS cases, using the El Escorial (EEC) and the Revised Airlie Diagnostic Criteria (AHC). The source of the study was a prospective population-based registry established in Puglia, southern Italy, in 1997. The diagnosis and the classification of the cases were based on EEC and AHC. All incident ALS cases during the period 1998–1999 were enrolled and followed up. During the surveillance period, we identified 130 ALS incident cases, and bulbar-ALS represented 20% of our cohort. The highest risk for bulbar onset was among subjects aged >75 years [RR: 20.1, 95% confidence interval (CI) 3.4–118.0] compared with subjects aged <55 years and among females compared with males (Relative risk (RR): 2.75, 95% CI: 1–7.3). The vast majority of patients (72%) referred progressive muscle weakness in the limbs as the presenting symptom. Eighty percent of cases presented contemporary bulbar or spinal involvement; UMN signs in the bulbar region were present in 24% of cases and any motoneuronal sign in thoracic region in only 15% of the cases. In this population-based series, progressive muscle weakness was the most common presenting sign; bulbar onset was associated with advanced age and female sex. UMN signs in the bulbar region and any motoneuronal sign in the thoracic region were observed in 20% of our case series. This may represent the main limitation to show the spread of signs during diagnostic assessment for inclusion in epidemiological studies and clinical trials.

Introduction

The diagnosis of amyotrophic lateral sclerosis (ALS) is made on clinical grounds, and requires the spread of both upper (UMN) and lower motoneuron (LMN) signs in different anatomic regions for entry in clinical trials [1,2]. The extreme variability of ALS clinical features at presentation may explain the delay in diagnosis and in case entry in clinical trials, especially outside ALS referral centers [1–3].

Clinical characteristics of ALS at presentation have been described mainly in clinical-based studies [2,4–6], compared with population-based studies [7–11]; population-based studies are probably more representative of the whole spectrum of the disease, compared with

clinical series from ALS tertiary centers. The aim of the study was to describe the symptoms and signs at diagnosis in a population-based incident cohort of ALS cases.

Material and methods

A prospective registry of all newly diagnosed ALS cases was established in Puglia, southern Italy, in 1997 [12]. The surveillance began on January 1, 1998. The registry had a multiple source system that is similar to the one used in the classical capture–recapture method, relying on five different sources:

- 1 A network of 23 neurological and neurophysiological facilities in the region.
- 2 The Hospital Discharge Diagnosis Data Bank, a regional computerized system including the diagnosis of each hospitalized patient in the area of the registry, both from public and private clinics.

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- 3 All facilities where EMG is performed in the region to also accept possible ALS outpatients that did not go through hospitalization.
- 4 The archives of AISLA, the lay Italian association of ALS.
- 5 The regional registry for riluzole prescription.

The diagnosis of ALS was based on the El Escorial criteria (EEC) [1] and their revised version of 1998 (AHC) [2]. Individuals under the age of 18 years were excluded to avoid misclassification of other motor neuron diseases of genetic origin. Using this multisource registry, we identified all newly diagnosed ALS cases resident in Puglia in the 2-year period from January 1, 1998 to December 31, 1999.

All patients were asked to give informed consent to participation in the study; data were stored in a centralized database and separate anonymous files were kept for each individual patient.

Results

During the 2-year surveillance period, we identified 130 ALS patients, including 81 males (62.3%) and 49 females (37.6%). Median age at diagnosis was 64.6 years overall, 65.4 years for males (range 19–80) and 64.2 years for females (range 28–80). The overall mean interval from first symptom to diagnosis was 14.4 months (range 1–70).

Limb onset was the most common presentation (Table 1; 74% of the cases). Patients with onset in lower limbs presented a tendency to refer a bilateral onset (51%). The site of symptom onset was primarily bulbar in 19% of all subjects (27% of women and 15% of men); 7% had a generalized onset.

The proportion of bulbar onset cases progressively increased with advancing age in both men and women; in fact, no bulbar ALS was diagnosed before the age of 45 years, whereas over the age of 75 years, the most common presentation was bulbar onset (58%; $P = 0.006$).

Table 1 Amyotrophic lateral sclerosis incident cases from a population-based registry: clinical site of onset

	Males (<i>n</i> = 81)	Females (<i>n</i> = 49)	Total (<i>n</i> = 130)
Limb			
Upper	27 (33)	19 (39)	46 (35)
Lower	28 (34)	15 (30)	45 (34)
Both	7 (9)	0	7 (5)
Bulbar	12 (15)	13 (27)	25 (19)
Generalized	7 (9)	2 (4)	9 (7)

Percentage values are given in parenthesis.

When we evaluated the risk of bulbar onset in a multivariate logistic regression model it was higher in subjects aged more than 75 years, compared to subjects aged < 55 years [RR: 20.1, 95% confidence interval (CI): 3.4–118.0] and in females compared with males (RR: 2.7; 95% CI: 1.0–7.3).

The vast majority of patients (72%) referred progressive muscle weakness as the presenting symptom with similar percentage in lower and upper limbs. Eighteen percent of cases presented fasciculations and 19% had muscle cramps; however, both symptoms were referred as the isolated symptom of onset in only 2% of the cases. Men were more likely than women to report cramps in this series (41% vs 14%; $P = 0.05$).

Twenty-three percent of cases reported difficulties in speaking and 11% dysphagia; in bulbar ALS, dysarthria was seven times more common than dysphagia as an isolated initial symptom (14 cases vs. 2).

Table 2 shows the neurological signs at presentation in every single region (bulbar, cervical, thoracic and lumbar) at the time of the diagnosis. The cervical and lumbar regions were the commonest sites at presentation (93% for both), followed by the bulbar (78%) and the thoracic regions (15%). A combined bulbar and spinal involvement was evident in 78% of our patients ($n = 101$). In upper and lower limbs we observed contemporary UMN and LMN signs in the 66% and 68% of the cases respectively, whereas solely UMN and LMN signs were uncommon.

As for the spinal regions, isolated UMN signs in the bulbar region were present in only one case while the combined presence of UMN and LMN signs at diagnosis was described in 24% of cases ($n = 31$). The most common bulbar UMN sign was spasticity, present in 35% of cases ($n = 11$), followed by clonic jaw (29%; $n = 9$), gag reflex (26%; $n = 8$), forced yawning (26%; $n = 8$) and pseudobulbar features (10% of the cases; $n = 3$). In the vast majority of cases (90%) the detection of UMN signs in the bulbar region was associated with a clinical picture of definite or probable ALS.

Table 2 Frequency of upper and lower motoneuron signs by region at diagnosis ($n = 130$)

Region	Bulbar (<i>n</i> = 101)	Cervical (<i>n</i> = 121)	Thoracic (<i>n</i> = 20)	Lumbar (<i>n</i> = 120)
UMN signs	1 (0.7)	9 (7)	7 (5)	10 (8)
LMN signs	70 (54)	26 (20)	5 (4)	22 (17)
Combined UMN + LMN signs	30 (23)	86 (66)	8 (6)	88 (68)

Percentage values are given in parenthesis

UMN, upper motor neuron; LMN, lower motor neuron.

Discussion

In this population-based study of incident ALS cases, bulbar-ALS represented 20% of our cohort; muscle weakness in the cervical and lumbar region was the commonest symptom at diagnosis; either UMN signs in bulbar region or any motoneuronal signs in the thoracic region were observed in a small percentage of our case series.

To our knowledge, after the studies in Ireland and northern Italy [8,9], this is the third population-based study looking at clinical features of ALS at presentation using the AHC and EEC in the diagnostic ascertainment of incident cases in a well-defined geographic area.

When we examined the site of onset of symptoms, limb onset was the most common (74.5% of the cases). The frequency of two types of presentation (bulbar and generalized ALS) (25.5%) resulted close to the frequency found in northern Italy (Piemonte/Valle D'Aosta and Lombardy) (31%) [9; E. Beghi, pers. comm.), but lower than those of the Irish study (more than 40%) [8]; bulbar ALS was more common among females and progressively increased with age in both men and women, resulting in the most common site of symptoms onset over the age of 70 years.

Because of the association between bulbar onset and advanced age, the higher percentage of bulbar ALS found in recent population based studies could be related to the older age at onset {63.7 years in Piemonte [9], 63.3 years in Ireland [8] and 64.6 years (this series in southern Italy)} compared with previous clinical series (55.7–58.6 years [4,6,13]).

The bulbar onset among the elderly may reflect a more aggressive course of the disease in the oldest age group and this could be confirmed by a shorter survivorship after diagnosis [10]. An alternative explanation could be that patients presenting with bulbar symptoms in extreme old age can more likely attract medical attention than those presenting with limb weakness.

Among cases with bulbar onset, dysarthria was seven times more common than dysphagia as the presenting symptom; this finding agrees with previous reports [6,8] and could be due to a selective vulnerability to the degenerative process of the glossal muscles rather than the deglutition muscles [14]. Another possible explanation is that mild difficulties in swallowing are more difficult to detect, especially in the oldest age group.

In almost 70% of the cases, combined UMN and LMN signs were present at diagnosis, whereas the isolated presence of UMN or LMN signs in all spinal regions was uncommon. These clinical findings agree with the results of the Irish study and support the

hypothesis that corticospinal tracts and anterior horns degeneration may happen at the same time [8,15].

Upper motoneuron signs in the bulbar region were detected at diagnosis in only 24% of the cases. Our results are consistent with a clinico-pathological study [16] that revealed UMN in the bulbar region in 20% of ALS patients at diagnosis and in 60% during the entire course of the disease. These findings indicate that the detection of UMN signs, particularly in the bulbar region, represents the main difficulty in the search for spread of signs in ALS cases, especially at the earliest stage of the disease [17].

In the thoracic region, both UMN and LMN signs were found in a small percentage of our patients (15%); LMN signs like weakness and atrophy of thoracic and abdominal muscles, as well as reduction of abdominal reflexes, are difficult to define, especially among elderly people. In addition, even if electromyogram (EMG) of paraspinal muscles should be a standard component of ALS work-up and is part of routine in tertiary centers, our population-based data show that was infrequently done in the routine EMG examinations in most of the territory comprised in our study. Because of these problems, the thoracic region rarely adds further evidence to the spread of signs that, in most cases, involve only three regions (bulbar, upper and lower limbs). None of our incident ALS cases showed spread of signs in four regions.

The strength of this study is that it is probably more representative of the whole spectrum of the disease, compared with the clinical series from ALS tertiary centers. The main limitation of our population-based study is the relatively small sample size compared with clinical series from tertiary centers.

The lack of detection of motoneuronal signs in the thoracic region and of UMN bulbar signs represents the main limitation in the search for spread of signs that is the prerequisite for the inclusion in clinical trials. The use of stringent criteria is probably useful in clinical trial where the likelihood of false positive cases should be minimized. A different approach would be probably useful for enrolment of ALS cases in epidemiological studies. All cases in which an appropriate diagnostic investigation excluded ALS mimic syndrome, after a minimum follow-up of 6 months, should be included and classified in a separate category even if the evidence of spread at first visit is limited at only one body region. This would be consistent with the category of suspected in the EEC.

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Appendix: Sclerosi Laterale Amiotrofica-Puglia (SLAP Registry)

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