Clinical Features of Amyotrophic Lateral Sclerosis According to the El Escorial and Airlie House Diagnostic Criteria

A Population-Based Study

Bryan J. Traynor, MD, MRCPI; Mary B. Codd, MD, PhD; Bernadette Corr, RSN; Colm Forde, MB; Eithne Frost, BA; Orla M. Hardiman, MD, MRCPI

Background: The El Escorial and the revised Airlie House diagnostic criteria for amyotrophic lateral sclerosis (ALS) classify patients into categories reflecting different levels of diagnostic certainty. We conducted a prospective, population-based study of the natural course of ALS in the Republic of Ireland during a 6-year period to examine the utility of these ALS diagnostic criteria.

Methods: Using data from the Irish ALS Register, we studied the clinical features of all patients diagnosed as having ALS in Ireland throughout their illness.

Results: Between 1993 and 1998, 388 patients were diagnosed as having ALS. Forty percent of patients reported bulbar-onset symptoms. Disease progression occurred over time: at last follow-up, 75% of all patients had bulbar signs, compared with 59% at diagnosis. When the El Escorial criteria were applied, more than half of patients (218 [56%]) had definite or probable ALS at diagnosis. Of the 165 possible and suspected ALS cases at diagnosis (trial ineligible), 110 (67%) were trial eligible at last follow-up. Of the 254 patients who had died, 229 (90%) had definite or probable ALS, whereas 25 patients (10%) remained trial ineligible at death. El Escorial category at diagnosis was not a significant prognostic indicator. Use of the Airlie House criteria had no effect on the median time from symptom onset to trial eligibility (12.9 vs 12.8 months).

Conclusions: The El Escorial and Airlie House diagnostic criteria are excessively restrictive. Furthermore, levels of diagnostic certainty cannot be used as prognostic indicators.

Arch Neurol. 2000;57:1171-1176
PATIENTS AND METHODS

The strength of this study lies in the existence of a complete register of all patients diagnosed as having ALS in Ireland. Details of this register have been published elsewhere. The vast majority of patients with ALS in Ireland are examined by a neurologist at some stage during their illness. Consequently, details of the medical care and clinical features provided to residents of the entire community are available for study, ensuring virtually complete case ascertainment of all cases of ALS occurring in this delineated population.

DIAGNOSTIC AND RESIDENCY CRITERIA

Diagnostic criteria for ALS were based on the EEC outlined by the World Federation of Neurology. These guidelines define 4 regions of the central nervous system, namely bulbar, cervical, thoracic, and lumbrosacral. A detailed attempt was made to exclude patients in whom symptoms are caused by conditions other than ALS (ie, ALS-mimic syndromes). Patients with suspected, possible, probable, and definite ALS according to the EEC were included in this study.

DATA COLLECTION AND FOLLOW-UP

Once patients with ALS are enrolled in the register, details of their initial clinical features are obtained either by review of their complete medical records or, where possible, examination of the patient. All patients enrolled in the register are routinely followed up during the course of their illness at intervals of not less than 4 months. This is achieved by several methods: by telephone conversation with the patient, primary care physician, and primary care neurologist and by direct examination of the patient by our group. Particular attention is given to functional status at diagnosis and follow-up, progression of clinical features, potential risk factors, family history of ALS, and causes of death. For the purposes of this study, every patient was followed up to at least March 1999. Apart from those who died, follow-up was complete to that date for 96% of patients.

STATISTICAL ANALYSIS

Data are stored on a computerized database (Microsoft Access, version 7.0; Microsoft Corporation, Seattle, Wash), allowing for organized retrieval of data. Statistical analyses are performed with SAS 6.11 statistical software. Survival was estimated by the Kaplan-Meier method and differences in survival were measured by log-rank sum test. Survival was examined for the cohort as a whole and separately for those with bulbar vs spinal onset and by the central nervous system (CNS) region involved. An analysis of the risk for death associated with selected independent variables used the Cox proportional hazard model. Calculations were performed by using the date of symptom onset as day 0. Statistical significance implies \( P < .05 \) unless otherwise stated.

The site of symptom onset of the population is shown in Table 1. Seventy-six (45%) of women and 61 (28%) of men initially had purely bulbar-onset disease. The proportion of bulbar-onset symptoms increased with advancing age.

Table 2 shows the frequency of neurological signs for (1) the whole cohort at the time of diagnosis and (2) the total cohort at last follow-up, as well as (3) those alive at last follow-up and (4) those who had died. Seventy-five percent of patients at last follow-up had bulbar signs, representing an increase of 19% compared with the time of diagnosis. A comparison of neurological signs by CNS region between those who were alive at last follow-up and those who had died suggested that bulbar regional involvement was more common among those who died (83% vs 60%).

The nature of the neurological signs found in each region is outlined in Table 3. Combined UMN and LMN signs were present in nearly 90% of all cases at death.

The EEC categories of the entire cohort at time of diagnosis are shown in Table 4. One third of ALS cases fulfilled the EEC for definite ALS, whereas 87 (22%) had probable ALS, 136 (35%) had possible ALS, and 29 (7%) had suspected ALS. Data on 5 patients were incomplete. Only 40% of patients with familial ALS fell into the definite category at the time of diagnosis.

At the time of last follow-up, two thirds of the total cohort had died or had received long-term mechanical ventilation. Ninety percent of the patients had clinical features consistent with either definite or probable ALS before death; 9% were classified as having possible ALS and 1% of deceased patients had suspected ALS (Table 4). The follow-up time for deceased patients with suspected or possible ALS was shorter than that of patients with probable or definite ALS (10.6 vs 13.2 months), whereas the time between last outpatient review and death was marginally longer (5.9 vs 3.4 months).

The EEC category of the entire cohort at time of last follow-up demonstrated a similar progression of clinical features and disability: the clinical features of more than 85% of patients had advanced sufficiently to allow reclassification as either definite or probable ALS, compared with a minority (14%) of patients who remained in the possible and suspected ALS categories.

Patients with limb-onset disease were more likely to be categorized as having definite ALS at diagnosis, whereas bulbar-onset symptoms were most frequently cat-
The Kaplan-Meier survival curves of Irish patients with ALS grouped according to their EEC category at diagnosis, at last follow-up, and at death are shown in Figure 1. The mortality rates of the 4 categories were similar (log rank test = 3.3; P = .51). Furthermore, the pattern of survival was similar in each diagnostic category. Median survival of patients in either the definite or probable category at diagnosis was 27 months, compared with 30 months for the possible category and 40 months for patients with suspected ALS. Multivariate analysis did not confirm EEC category at diagnosis as an independent predictor of prognosis.

The EEC for definite or probable ALS have been applied for inclusion in clinical trials.2-4 When the current practice was applied to the Irish cohort, the median time from symptom onset to trial eligibility was 13 months, compared with 11 months in the AHC.3 Two hundred eighteen patients (56%) would have been considered trial eligible at diagnosis, whereas sex ratio, duration of follow-up, and median survival were statistically similar among trial-eligible and trial-ineligible patients.

Table 2. Frequency of Clinical Signs in Each El Escorial Region of the Irish Patients With Amyotrophic Lateral Sclerosis at Diagnosis, and at Death, 1993 Through 1998

<table>
<thead>
<tr>
<th>Region</th>
<th>Total Cohort at Diagnosis (n = 383)*</th>
<th>Total Cohort at Last Follow-up (n = 383)*</th>
<th>Alive at Last Follow-up (n = 130)*</th>
<th>Dead at Last Follow-up (n = 253)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulbar</td>
<td>213 (56)</td>
<td>209 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>264 (69)</td>
<td>176 (70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>227 (59)</td>
<td>206 (81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar</td>
<td>284 (74)</td>
<td>222 (88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ALS indicates amyotrophic lateral sclerosis; UMN, upper motor neuron; and LMN, lower motor neuron.
- Patients may have had more than 1 region involved; percentages refer to each region.
- Excludes 5 patients for whom data were incomplete.
- Excludes 1 patient with incomplete data and 1 patient who received mechanical ventilation.

The Kaplan-Meier survival curves of Irish patients with ALS grouped according to their EEC category at diagnosis, at last follow-up, and at death are shown in Figure 1. The mortality rates of the 4 categories were similar (log rank test = 3.3; P = .51). Furthermore, the pattern of survival was similar in each diagnostic category. Median survival of patients in either the definite or probable category at diagnosis was 27 months, compared with 30 months for the possible category and 40 months for patients with suspected ALS. Multivariate analysis did not confirm EEC category at diagnosis as an independent predictor of prognosis.

The EEC for definite or probable ALS have been applied for inclusion in clinical trials.2-4 When the current practice was applied to the Irish cohort, the median time from symptom onset to trial eligibility was 13 months (Figure 2). Two hundred eighteen patients (56%) would have been considered trial eligible at the time of their diagnosis. Of the remaining 169 patients (136 possible, 29 suspected [43%]) who were trial ineligible at diagnosis, two thirds (110) became eligible during the follow-up period. The remaining 55 patients with ALS (14%) either had died of their neurological condition without being considered trial eligible (3 suspected, 22 possible) or had not changed diagnostic category from the time of diagnosis (6 suspected, 24 possible).

Potentially modifying factors were examined for their influence on trial eligibility under the EEC guidelines: bulbar-onset symptoms were associated with an earlier trial inclusion compared with limb-onset disease (11 vs 15 months; P = .001; Figure 2), whereas sex ratio, duration of follow-up, and median survival were statistically similar among trial-eligible and trial-ineligible patients.

When the AHC were applied, there was little difference in the number of patients considered eligible for clinical trials or the time for an individual patient to be-
This study is, to our knowledge, the second prospective population-based study of ALS survival and the first to identify all cases in an entire country during an extended period. Survival from diagnosis at 1, 3, and 5 years was 68%, 25%, and 17%, respectively, and there was evidence of disease progression both in the number of CNS regions involved and in the nature of involvement in each region. It is also the first epidemiological study of ALS, to our knowledge, to use the EEC for diagnosis and follow-up of patients, thus allowing for standardized comparison with future epidemiological and clinical studies.

More than 40% of the patients with ALS had bulbar or generalized symptoms at symptom onset, which is higher than some previously reported. However, other studies with complete case ascertainment have reported similar findings, suggesting that the high rate of bulbar-onset symptoms reflects the true disease distribution.

Our findings would suggest that cases with bulbar onset are first seen at an earlier stage in the disease process, before spread to other CNS regions has occurred. In the bulbar-onset population, dysarthria was 8 times more common than dysphagia as an initial symptom. This finding agrees with previous reports and may suggest that the glossal musculature is more vulnerable to the neurodegenerative process than the deglutition muscles. Alternatively, dysarthria may be reported more commonly by patients with ALS and their caregivers because slurred speech is easier to recognize than mild swallowing difficulties. This highlights the importance of obtaining an adequate intake history, including choking episodes; subtle changes in dietary consistency, such as avoidance of certain foods; duration of meals; and measurable weight loss.

The frequency of neurological signs in all 4 regions increased dramatically during the course of the illness. Our findings indicate that the majority of patients with ALS progress to have generalized involvement by the time of death. The pattern of UMN and LMN signs was similar in each region both at diagnosis and at death, ie, combined UMN and LMN signs accounted for the majority of cases, whereas solely UMN or LMN signs were comparatively uncommon. This supports the observation that corticospinal tract degeneration and anterior horn cell death may be linked and infrequently occur in isolation.

Slightly more than half of Irish patients with ALS had either definite or probable ALS by EEC at the time of diagnosis and were eligible for clinical trial inclusion. There are few previous reports of the EEC categories of patients at time of diagnosis with which to compare our results. Although they did not strictly apply EEC, Haverkamp et al reported that 9% of 1200 patients attending a specialist ALS clinic had solely LMN signs (corresponding to suspected ALS), 3% had only UMN signs (ie, possible ALS), and 831 patients (69%) had “typical ALS.” In a clinicopathological study of the EEC in 32 cases of ALS, only 10 patients (31%) carried a diagnosis of definite or probable ALS at initial examination.

In our study, approximately 10% of those who died of their disease were still classified as having suspected or possible ALS at the time of their death and were thus considered ineligible for clinical trials. The length of follow-up and the time from last review to death differed by only 2 months between the 25 trial-ineligible patients and the total cohort. Furthermore, the demographic characteristics of those who died did not differ significantly from those of the entire cohort, suggesting that their inability to travel was a function of their progressive disability. Although we were unable to have autopsies performed on our deceased patients, telephone and, often, personal contact between the patient and the ALS team was maintained until the time of death. We conclude, therefore, that those 25 patients died of ALS, albeit without reaching a stringently defined “certainty” with respect to their diagnosis.

Our findings have demonstrated that the EEC category of patients with ALS at diagnosis does not predict
prognosis. One possible explanation for this unexpected finding may lie in the arbitrary and artificial definitions of the EEC categories and CNS regions. For example, a patient with subclinical electromyographic findings or fasciculations and mild weakness in a limb is considered to exhibit the same level of diagnostic certainty as another patient with profound weakness and atrophy in the same area, although the “disease burden” clearly differs between the 2 patients. Future diagnostic criteria for ALS that incorporate a role for quantitative muscle strength testing or neurophysiological estimation of spinal motor neuron burden would be helpful to reflect the extent of disease.

Currently, patients with ALS who have only LMN signs are excluded from clinical trials, and the suspected category has been deleted from the revised EEC. Our study demonstrates that patients with suspected ALS at diagnosis have a clinically similar course to patients in the other ALS categories: survival of the 29 patients with suspected ALS at diagnosis was statistically similar to patient survival in other EEC or AHC categories (Figure 1). As only 3 of the 254 deceased Irish patients with ALS had clinical features of primary lateral sclerosis at time of death, it is apparent that the majority of patients with only LMN signs at an early stage ultimately progress to other categories. Two of these cases proceeded to autopsy, of which one was an autopsy-proven case in a 74-year-old woman. The other was in a 54-year-old man without clinical UMN signs before death, but postmortem examination disclosed corticospinal involvement. The postmortem finding of ubiquinated neuronal inclusions, the pathological hallmark of ALS, in several cases of primary lateral sclerosis strengthens the view that the clinical diagnosis of primary lateral sclerosis represents ALS. Furthermore, patients with superoxide dismutase 1 mutations are known to initially manifest solely LMN findings and are included as having clinically definite familial, laboratory-supported ALS. Until the underlying pathogenic mechanisms of ALS are more fully understood, we believe that current evidence supports the inclusion of primary lateral sclerosis and suspected ALS that is clearly progressing in clinical trials.

Our findings indicate that use of the stringent EEC and AHC decreases the possibility of ALS misdiagnosis but also necessitates that patients have widespread disease to be considered eligible for trials. The difference in the time from disease onset to trial eligibility between the old EEC and the new AHC (median time, 12.8 vs 12.9 months) was small, and there was a greater than 99% agreement between the classification systems. This suggests that the revised guidelines did not succeed in their aim of shortening the time to trial eligibility. Therefore, the advantage of the EEC and AHC is that they prevent the inclusion of patients with ALS-mimic syndromes, who tend to have a better prognosis than patients with ALS. However, our previous findings demonstrate that patients with mimic syndromes can be excluded by appropriate prediagnostic investigations and by monitoring patients over time. The current criteria, which are based on the likelihood of a patient suffering from the disease by determining the extent of clinically apparent abnor-

Clinical diagnosis of primary lateral sclerosis represents to reflect the extent of disease.21,22 Muscle strength testing or neurophysiological estimation of muscle strength testing or neurophysiological estimation of spinal motor neuron function in the same area, although the “disease burden” clearly differs between the 2 patients. Future diagnostic criteria for ALS that incorporate a role for quantitative muscle strength testing or neurophysiological estimation of spinal motor neuron burden would be helpful to reflect the extent of disease.

Clinical diagnosis of primary lateral sclerosis represents to reflect the extent of disease.21,22 Muscle strength testing or neurophysiological estimation of muscle strength testing or neurophysiological estimation of spinal motor neuron function in the same area, although the “disease burden” clearly differs between the 2 patients. Future diagnostic criteria for ALS that incorporate a role for quantitative muscle strength testing or neurophysiological estimation of spinal motor neuron burden would be helpful to reflect the extent of disease.

Clinical diagnosis of primary lateral sclerosis represents to reflect the extent of disease.21,22 Muscle strength testing or neurophysiological estimation of muscle strength testing or neurophysiological estimation of spinal motor neuron function in the same area, although the “disease burden” clearly differs between the 2 patients. Future diagnostic criteria for ALS that incorporate a role for quantitative muscle strength testing or neurophysiological estimation of spinal motor neuron burden would be helpful to reflect the extent of disease.

We gratefully acknowledge the assistance of all the consultant neurologists, neurophysiologists, and primary care physicians who collaborate in recruitment for the register. We also thank the Irish Motor Neuron Disease Association and the Irish Brain Research Foundation for their support. Reprints: Orla M. Hardiman, MD, MRCPI, Department of Neurology, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland (e-mail: ohard@iol.ie).

Accepted for publication February 4, 2000.
REFERENCES


16. Bisiach E, Vallar G, Perani D, Papagno C, Berti A. Unawareness of disease fol-
17. Feinberg TE, Haber LD, Stacy CB. Ipsilateral extinction in the hemineglect syn-
18. Di Pellegrino G, De Renzi E. An experimental investigation of the nature of
19. Frenay C, Beis JM, Rode G, Boisson D, Andre JM, Eysette M. Place de l’extinction
21. Vigouroux RA, Bonnefoi B, Khalil R. Re´alisations picturales chez un artiste pe-
23. Cantagallo A, Della Sala S. Preserved insight in an artist with extrapersonal spa-
25. Rode G, Perenin MT, Honor´o J, Boisson D. Improvement of the motor deficit of
neglect patients through vestibular stimulation: evidence for a motor neglect com-
26. Rode G, Perenin MT. Temporary remission of representational heminegligence through
27. Schilder P. The Image and Appearance of the Human Body. New York, NY: Inter-
32. Kinsbourne M. Orientation bias model of unilateral neglect: evidence from at-
tentional gradients within hemispace. In: Robertson HH, Marshall JC, eds. Uni-

Correction

Error in Text. In the Original Contribution by Traynor et al titled “Clinical Features of Amyotrophic Lateral Sclerosis According to the El Escorial and Airlie House Diagnostic Criteria: A Population-Based Study,” published in the August issue of the Archives (2000;57:1171-1176), 4 errors occurred in the second paragraph on page 1175. The words primary lateral sclerosis should have read progressive muscular atrophy in the 10th, 20th, 21st, and 28th lines of this paragraph. The paragraph should have read as follows: “Currently, patients with ALS who have only LMN signs are excluded from clinical trials, and the suspected category has been deleted from the revised EEC.2 Our study demonstrates that patients with suspected ALS at diagnosis have a clinically similar course to patients in the other ALS categories: survival of the 29 patients with suspected ALS at diagnosis was statistically similar to patient survival in other EEC or AHC categories (Figure 1). As only 3 of the 254 deceased Irish patients with ALS had clinical features of progressive muscular atrophy at the time of death, it is apparent that the majority of patients with only LMN signs at an early stage ultimately progress to other categories. Two of these cases proceeded to autopsy, of which one was an autopsy-proved case in a 74-year-old woman. The other was in a 54-year-old man without clinical UMN signs before death, but postmortem examination disclosed corticospinal involvement. The postmortem finding of ubiquinated neuronal inclusions, the pathological hallmark of ALS,21 in several cases of progressive muscular atrophy strengthens the view that the clinical diagnosis of progressive muscular atrophy represents ALS.30 Furthermore, patients with superoxide dismutase 1 mutations are known to initially manifest solely LMN findings36 and are included as having clinically definite familial, laboratory-supported ALS.34 Until the underlying pathogenic mechanisms of ALS are more fully understood, we believe that current evidence supports the inclusion of progressive muscular atrophy and suspected ALS that is clearly progressing in clinical trials.”