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ORIGINAL RESEARCH

Survival benefit of multidisciplinary care in amyotrophic lateral sclerosis in Spain: association with noninvasive mechanical ventilation

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Purpose: Multidisciplinary care has become the preferred model of care for patients with amyotrophic lateral sclerosis (ALS). It is assumed that the sum of interventions associated with this approach has a positive effect on survival. The objective of the study was to evaluate the impact of a multidisciplinary care approach on the survival of patients with ALS.

Patients and methods: We performed a retrospective review of prospectively collected data in a tertiary referral center in Spain. Participants were patients with definite or probable ALS managed in a multidisciplinary care program. We compared demographic and survival data of patients with definite or probable ALS treated in a referral center without and with implementation of a multidisciplinary care program. We performed time-dependent multivariate survival analysis of the use of noninvasive mechanical ventilation (NIMV) and gastrostomy.

Results: We evaluated 398 consecutive patients, of whom 54 were treated by a general neurologist and 344 were treated in the multidisciplinary care clinic. Patients receiving multidisciplinary care were older (62 vs 58 years), tended to have bulbar onset disease (30% vs 17.7%), and were more likely to receive riluzole (88.7% vs 29.6%, $p<0.01$), NIMV (48.8% vs 29.6%, $p>0.001$), and nutrition via gastrostomy (32.3% vs 3.7%, $p<0.01$). Kaplan–Meier analysis showed a 6-month increase in survival (log-rank, 16.03, $p<0.001$). Application of the Andersen-Gill model showed that the variables associated with reduced mortality were reduced time to NIMV and gastrostomy and the duration of both, thus reflecting compliance.

Conclusions: Multidisciplinary care increased the survival of ALS patients in our study population. Timely use of respiratory support and gastrostomy are fundamental aspects of this benefit.

Keywords: ALS, survival, multidisciplinary care, noninvasive mechanical ventilation, gastrostomy

Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder characterized by progressive loss of neurons. It affects the corticospinal tract, brainstem, and anterior horn cells of the spinal cord, leading to loss of bulbar and limb function and respiratory muscle weakness.[1] Mean life expectancy is 3–5 years, although this varies considerably, with up to 10% of patients living longer than 10 years.[2]

Despite numerous clinical trials, riluzole continues to be the only approved pharmacological agent and has been shown to prolong survival by around 38% at 18 months.[3] Therefore, treatment of ALS is aimed at relieving symptoms and

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improving quality of life (QoL). Multidisciplinary care is the standard approach recommended by guidelines from Europe[4] and the US.[5] This approach was first shown to improve survival in Ireland,[6] with subsequent reports from Italy[7] and England,[8] all of which pointed to an association between increased use of riluzole, gastrostomy, and non-invasive mechanical ventilation (NIMV) and longer survival. There is also evidence that multidisciplinary care improves QoL.[9] However, not all reports have shown a positive effect. A study from southern Italy showed no improved survival in a cohort of patients treated based on a multidisciplinary approach in whom the use of gastrostomy and NIMV was infrequent.[10] Furthermore, survival studies have been criticized because patients referred for multidisciplinary care are young and therefore have good survival prospects.[11]

We describe our experience with the implementation of a program for the multidisciplinary care of ALS patients at a referral center in Spain. We also evaluated clinical variables associated with prognosis, focusing on the impact of NIMV and duration of gastrostomy tube placement on survival.

Materials and methods

The ALS Multidisciplinary Care Clinic at Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain was established in 2001 to ensure delivery of continuing care through a dedicated team of specialists (neurologist, pulmonologist, nutritionist, endocrinologist, rehabilitation specialist, physical therapist, psychologist, social worker, nurse manager, speech therapist, and an administrative worker). Patients were seen every 3 months, with each visit including assessment of pulmonary function (forced spirometry; home nocturnal pulse oximetry; and arterial blood gas levels) and nutritional status, with early NIMV and placement of a gastrostomy tube advocated as stated in the guidelines of the American Academy of Neurology and the European Federation of Neurological Societies.[4,5]

From January 2001 to December 2012, we prospectively collected the following data from each new patient with probable or definite ALS admitted to the clinic: symptom onset, date of diagnosis, type of onset (bulbar, spinal, respiratory), and demographic characteristics. In addition, we retrospectively reviewed our local database and the hospital records of 54 patients seen by a neuromuscular neurologist during the previous 10 years (1991–2000) and who met the criteria for probable or definite ALS. We recorded family history of ALS and the diagnostic delay from symptom onset, as these are well-established prognostic factors.[12] Survival was measured in months from symptom onset. In order to ensure comparability between the groups and exclude historic control long-term survivors who may have been seen at the clinic later in the course of their disease, we excluded those controls whose period from symptom onset to death overlapped with implementation of multidisciplinary care. We also reviewed each file individually and excluded patients with atypical motor neuron disease phenotypes (primary lateral sclerosis, primary muscular atrophy, flail arm syndrome, flail leg syndrome, Kennedy disease), as these patients are long-term survivors within the motor neuron disease spectrum. Follow-up was managed using the registry of the ALS patients' association (Fundación Miquel Valls) and review of centralized primary care information.

Statistical analysis

We report the demographic and clinical characteristics of both groups as means for age (with range or standard deviation values, as appropriate) and as percentages for categorical variables. Normally distributed continuous variables were compared using the *t* test; non-normally distributed variables were compared using the Mann–Whitney test. Proportions were compared using χ^2 test. Survival curves were constructed using the Kalbfleisch–Prentice method,[13] which is equivalent to the Kaplan–Meier estimates when the weights are unity (as in our case). Survival curves were compared using the log-rank test.[14] Multivariate analyses were performed using the Andersen–Gill model.[15–17] Explanatory variables included age, sex, site of onset, family history, use of riluzole, NIMV, gastrostomy, and treatment at the multidisciplinary care clinic. Explanatory variables in the risk of progression of ALS that are time-dependent include time on NIMV and duration of gastrostomy tube placement. Risks are therefore not proportional and violate the main assumption of the Cox proportional hazard risks model. For this reason, and in order to obtain consistent estimates, the Andersen–Gill model was used, allowing for the evaluation of time-dependent variables that could account for the risk of progression of ALS.

To further explore how multidisciplinary care affected survival, we calculated time from symptom onset to NIMV and gastrostomy, as well as the time each patient received NIMV, and used gastrostomy as a measure of tolerance and compliance. The descriptive analysis, Kalbfleisch–Prentice

estimation of the survival curves, and the log-rank test were performed using IBM SPSS Statistics for Windows, version 21.0. The multivariate analyses were carried out in the free statistical software environment R, version 3.2.1. A value of $p>0.05$ was deemed statistically significant, and comparative tests were two-tailed.

Results

We prospectively followed up 334 ALS patients in our multidisciplinary care clinic from January 2001 to December 2012. Demographic data are shown in Table 1. As expected, there was a predominance of men, who were slightly overrepresented in the historic control patients (64.8% vs 53.6%, $p=0.14$). Patients treated in the clinic were older (62 vs 58 years, $p=0.01$), with a trend toward a more frequent bulbar onset, although without reaching statistical significance (30.9 vs 17.7%, $p=0.35$). Patients treated in the clinic were more likely to receive interventions such as riluzole (88.7% vs 30.6%, $p<0.001$), NIMV (47.8% vs 14.5%, $p<0.001$), and gastrostomy (32.9% vs 3.2%, $p<0.001$). In patients receiving NIMV, multidisciplinary care was associated with a significant shortening of the time to NIMV (14 vs 25 months, $p<0.001$). Patients in the historic cohort had a 2-month shorter mean diagnostic delay (8 vs 10 months, $p=0.15$).

Survival analyses

A total of 276 patients (30.7%) died during follow-up. Median survival time was 34 months (95% CI, 27–41) for the historic cohort and 40 months (95% CI, 35–45) for those treated under the multidisciplinary care model. This difference was statistically significant (log-rank, $p<0.001$). The increase in survival was greater in patients with bulbar onset disease, where survival increased by 10 months (24 vs 34 months; log-rank, 9.07; $p=0.003$).

Application of the Andersen–Gill models showed that bulbar onset and older age were associated with a poorer prognosis, while the use of riluzole was protective (Table 2). In this model, multidisciplinary care showed a nonsignificant trend toward a protective effect (HR, 0.37; 95% CI, 0.034–4.08; $p=0.41$). None of the other therapeutic interventions were associated with reduced mortality. However, when time of gastrostomy and NIMV were included in the model as time-dependent covariables, we found that the use of both interventions was directly associated with reduced mortality (Table 3). Likewise, the time from symptom onset to NIMV and gastrostomy were independent protective factors, with each month of NIMV representing a 6% decrease in mortality hazard and each month of gastrostomy representing a 3% decrease.

Discussion

Over the past two decades, multidisciplinary care has become the preferred model of care for ALS patients worldwide. Centralization in tertiary care centers provides several advantages for both patients and the ALS research community. A multidisciplinary approach allows concentration of caregiver expertise in an infrequent disease, better communication between team members (thus facilitating decision-making and planned advanced directives, faster and timely access to interventions [pharmacological, nutritional, respiratory, and physiotherapeutic]), and easier access to research and clinical

Table 1 Clinical and demographic characteristics

	Neurology clinic n=54	Multidisciplinary care clinic n=344	*p*-value
Age at onset in years (range)	58 (30–77)	62 (24–87)	0.01
Gender	M: 35 (64.8%)	M: 183 (53.6%)	0.14
Type of onset			
Spinal	41 (75.9%)	229 (66.65%)	0.35
Bulbar	11 (20.4%)	103 (29.9%)	
Respiratory	2 (3.7%)	12 (3.5%)	
Riluzole	16 (29.6%)	305 (88.7%)	<0.001
NIMV	7 (13%)	168 (48.8%)	<0.001
Gastrostomy	2 (3.7%)	111 (32.3%)	<0.001
Family history	2 (3.2%)	4 (1.1%)	0.20
Time to NIMV (months)	25	14	<0.001
Diagnostic delay (months)	8	10	0.15

Abbreviation: NIMV, noninvasive mechanical ventilation.

Table 2 Andersen–Gill multivariate analysis

Variable	Hazard ratio	95% CI	*p*-value
ALS unit	0.37	0.034–4.08	0.41
Gender	0.98	0.76–1.27	0.91
Bulbar onset	1.07	0.78–1.46	0.67
Family history	0.44	0.84–5.91	0.1
Riluzole	0.57	0.44–0.92	0.01
NIMV	0.8	0.94–1.63	0.12
Gastrostomy	0.78	0.94–1.7	0.11
Age (years)	1.02	1.01–1.03	<0.001
Diagnostic delay (months)	1.01	0.98–1.01	0.14

Abbreviation: NIMV, noninvasive mechanical ventilation.

Table 3 Andersen–Gill multivariate analysis with time depending covariables

Variable	Hazard Ratio	95% CI	*p*-value
ALS Unit	0.88	0.07–10.12	0.92
Gender	0.90	0.86–1.42	0.42
Bulbar onset	2.43	1.24–4.77	0.01
Family history	1.54	0.59–3.98	0.37
Riluzole	0.82	0.44–0.92	0.01
NIMV	2.7	1.94–3.8	0.12
Gastrostomy	1.83	1.29–2.58	<0.001
Age (years)	1.02	1.01–1.03	<0.001
Diagnostic delay (months)	0.99	0.99–1.0	0.71
Time of NIMV use (months)	0.94	0.93–0.94	<0.001
Time of gastrostomy use (months)	0.97	0.95–0.98	<0.001

Abbreviation: NIMV, noninvasive mechanical ventilation.

trials. Although a cumulative body of evidence shows that multidisciplinary care results in increased patient life span,[18,19] the factor accounting most for this increase in survival remains unknown. Some initial reports suggested that this may be due to referral bias,[9] although more recent population-based research in Ireland has consistently demonstrated that multidisciplinary care confers a survival advantage that is independent of age in patients with ALS.[20]

To the best of our knowledge, this is the first study to evaluate the effect of a multidisciplinary care model in Spain. Our study provides further evidence for increased survival in the multidisciplinary care clinic compared with a general neurology practice. Patients with bulbar disease are those who most benefit from a multidisciplinary approach. In our center, patients receiving multidisciplinary care were more likely to receive interventions destined to increase survival. Given that use of riluzole,[3] NIMV,[21] and nutritional support have all been associated with increased survival, it is difficult to establish the role of each intervention on the observed effect.

The effect of compliance with NIMV has been associated with improved survival in the context of multidisciplinary care.[22] The Andersen–Gill model better reflects the effect of time-dependent variables on survival, as it provides data from discontinuous intervals of risk. Using this model, we were able to establish a relationship between a reduced time from symptom onset to NIMV and gastrostomy and improved survival. However, it is important to remember that procedures were often undertaken later than necessary. This is not surprising, given that the control cohort includes patients who were diagnosed 20–30 years ago. The model also allowed us to include duration of NIMV and gastrostomy tube placement as variables, which in both cases revealed a protective effect. We hypothesize that the extent of this period reflects factors such as improved tolerability, patient compliance, and caregiver support. In fact, when included in the model, adherence to NIMV and gastrostomy remain protective. However, the need for gastrostomy or NIMV, which reflect an aggressive later-stage approach in patients with early bulbar disease or respiratory onset, is associated with a poorer prognosis.

Use of historic controls allowed us to better reflect the impact of multidisciplinary care on patients with ALS, although it also highlighted limitations, since these only reflect the practice of a single neurologist. In addition, their retrospective nature makes it impossible to control for unknown variables, and the fact that the patients were from different time periods could generate bias resulting from changes in management protocols. There is also the presence of collinearity in the time-dependent variables, because controls less frequently received NIMV and gastrostomy. We strongly believe that time-dependent variables should be included in future prospective analyses: our results provide evidence that they significantly affect the survival of ALS patients receiving multidisciplinary care. In contrast with other studies, patients attending the multidisciplinary unit were not necessarily younger. In addition, the impact of age on survival is greater in patients with bulbar involvement, most likely owing to the early management of dysphagia-associated complications. Even so, analysis of the impact of the unit does not reveal variations, probably because the disease has a poorer prognosis in these patients. Our results are also limited by the fact that we were unable to include cognitive impairment as a prognostic variable, since

a neuropsychological evaluation was not systematically performed at the time. The limitations of this study could be improved by performing studies with larger numbers of patients and, therefore, larger databases.

Possible advantages of the multidisciplinary care approach not assessed in this cohort include psychosocial advantages in terms of communication with primary care teams, caregiver support, reduced hospital admissions, and earlier referral for palliative care. We believe these interventions might have an added effect on the survival of ALS patients and should be studied prospectively.

Conclusion

Implementation of multidisciplinary care resulted in improved survival in our ALS population. Timely use of NIMV and gastrostomy and compliance with interventions are fundamental aspects of this benefit and deserve evaluation in further prospective studies.

Compliance with ethical standards

The study was reviewed and approved by the Clinical Investigation Ethics Committee of the Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain. Patient consent was obtained in compliance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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