Amyotrophic Lateral Sclerosis: Impact of Pulmonary Follow-Up and Mechanical Ventilation on Survival. A Study of 114 Cases

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Abstract

Objective: To study the impact of ventilatory management and treatment on the survival of patients with amyotrophic lateral sclerosis (ALS).

Method: Retrospective analysis of 114 consecutive patients admitted to a general hospital, evaluating demographic data, type of presentation, clinical management, treatment with mechanical ventilation and survival. Statistics: descriptive and Kaplan–Meier estimator.

Results: Sixty-four patients presented initial bulbar involvement. Overall mean survival after diagnosis was 28.0 months (95% CI, 21.1–34.8). Seventy patients were referred to the pulmonary specialist (61.4%) and 43 received non-invasive ventilation (NIV) at 12.7 months (median) after diagnosis. Thirty-seven patients continued to receive NIV with no subsequent invasive ventilation. The mean survival of these patients was 23.3 months (95% CI, 16.7–28.8), higher in those without bulbar involvement, although below the range of significance. Survival in the 26 patients receiving programmed NIV was higher than in the 11 patients in whom this was indicated without prior pulmonary assessment (considered following diagnosis, P<0.02, and in accordance with the start of ventilation, P<0.04). A total of 7 patients were treated invasively; mean survival in this group was 72 months (95% CI, 14.36–129.6), median 49.6±17.5 (95% CI, 15.3–83.8), and despite the difficulties involved in home care, acceptance and tolerance was acceptable.

Conclusions: Long-term mechanical ventilation prolongs survival in ALS. Programmed pulmonary assessment has a positive impact on survival of ALS patients and is key to the multidisciplinary management of this disease.

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Resumen

Objetivo: Conocer el impacto en la supervivencia del manejo y tratamiento ventilatorio de enfermos con esclerosis lateral amiotrófica (ELA). Método: Análisis retrospectivo de 114 pacientes con ingreso consecutivo en un hospital general, evaluando datos demográficos, tipo de presentación, manejo clínico, tratamiento con ventilación mecánica y supervivencia. Estadística: descriptiva y análisis de Kaplan-Meier.

Resultados: Sesenta y cuatro pacientes tenían afectación bulbar inicial. La supervivencia media global tras el diagnóstico fue 28.0 meses (IC 95%, 21.1–34.8). Setenta pacientes fueron derivados al neumólogo (61.4%) y 43 recibieron ventilación no invasiva (VMNI) a los 12.7 meses (mediana) del diagnóstico. Se mantuvieron con VMNI sin posterior ventilación invasiva 37 pacientes, cuya supervivencia media fue de 23.3 meses (IC 95%, 16.7–28.8), superior en los no bulbares, aunque en rango no significativo. En 26 en los que la VMNI se indicó de manera programada la supervivencia fue mayor que en 11 en que se indicó sin evaluación neumológica previa (considerando tras el diagnóstico, p<0.012, y en función del comienzo

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Introducción

La esclerosis lateral amiotrófica (ALS) es caracterizada por debilidad muscular y progresiva parálisis, y es la forma más común de enfermedad de motor neuromuscular. La incidencia se estima que es de 1-2 casos por cada 100 000 habitantes/año: 5%-10% de los casos son de forma familiar, y la mayoría es de forma espasmódica.\(^1\)\(^-\)\(^3\) Es causado por la progresiva pérdida de neuronas motoras en el tronco medular, músculos bulbares y el cordón espinoso, conduciendo a debilidad y parálisis de los músculos de los miembros superiores y inferiores, cara y tronco, incluyendo el diafragma.\(^4\) La presentación es heterogénea, con variable involucramiento de los grupos musculares y diferentes mecanismos en función del diagnóstico y de la calidad de vida, probablemente reflejando los diferentes mecanismos causantes. El bulbar y el respiromotor involucra la disartria, tos, tos ineficaz, disnea, ortopnea y respuestas ventilatorias respiratorias, generalmente conduciendo a la muerte entre 3-5 años después de la enfermedad.\(^1\)\(^-\)\(^5\)

Las opciones de tratamiento son muy limitadas. Se puede usar riluzol, pero su uso es limitado y débil,\(^6\) y las únicas medidas terapéuticas realistas que son paliativas. La mayoría de los tratamientos son invasivos (NIHV).\(^1\)\(^-\)\(^3\) La NIV se puede usar en el hogar, el equipo se hace amigable y controla la respiración de forma que es bien aceptado por los pacientes y los cuidadores. Como la enfermedad avanza, y cuando se nota el involucramiento del bulbo, la NIV se considera insuficiente y la ventilación invasiva durante traqueostomía se debe considerar.\(^1\)\(^-\)\(^3\)

En adición a la enfermedad respiratoria, los pacientes desarrollan cambios significativos en su capacidad para moverse y comunicarse, junto con nutrición y discapacidad social, enfermedad de trabajadores y cuidadores para proporcionar la atención respiratoria necesaria para el tratamiento de la enfermedad respiratoria.\(^1\)\(^-\)\(^3\) Con el fin de definir el papel del pulmonólogo especialista en el multidisciplinario de la atencion de los pacientes, hemos examinado la utilidad de los procedimientos de cuidado respiratorio programados y el impacto de la ventilación mecánica en el sigilo de los pacientes atendidos en un hospital general con un servicio de ALS especializado.

Material y Métodos

Selección y tratamiento

Hicimos una revisión retrospectiva de la atención de los pacientes con diagnóstico de ALS consecutivamente hospitalizados en nuestro centro entre el 1 de enero de 2000 y 31 de diciembre de 2010. Se trata de un nivel III hospital con un área de captación de 550 000 habitantes. El cuidado inicial de los pacientes con sospecha de ALS en este periodo no se incluyó en la referencia de un pulmonólogo para evaluación de necesidades ventilatorias, y los pacientes con diagnóstico de ALS (CIE-9:335.20) se identificaron a partir de los expedientes hospitalarios. Se incluyeron los pacientes con diagnóstico de ALS determinado por un pulmonólogo según los criterios de la Sociedad Española de Neumología. La lista inicial de 180 pacientes recibieron el tratamiento hospitalario y se excluyeron los pacientes que fueron excluidos debido a que tenían procesos neuromusculares distintos a ALS o porque fueron tratados en cuidados intensivos no asociados con nuestro hospital. Los casos con ALS no sólo en el ámbito hospitalario y no hospitalizado también se excluyeron. Los pacientes que, al comienzo o durante el curso de su enfermedad, tuvieron dificultad con la fonación o tos recidivante, confirmado por ambos pulmonólogo y neumólogo, se clasificaron como casos de ALS.

Después de la valoración, todos los pacientes con enfermedad respiratoria, según los criterios establecidos,\(^1\)\(^-\)\(^3\) se ofrecieron un dispositivo de ventilación invasiva. La ventilación invasiva (VS) ultra y VS III se usó en el modo asistido independiente (ST) y en el modo presión de soporte (PSV) con una nariz o branquial. La ventilación se realizó con el paciente hospitalizado o en el ámbito ambulatorio, iniciándose con la presión respiratoria más baja hasta que el paciente estaba relajado. Oxígeno y gases para la ventilación de cuidados intensivos fueron supervisados durante los periodos de vigilia y oxímetro de dedo.

Los pacientes hospitalizados se monitorearon por el físico- terapéutico y el hospitalizante de la unidad de cuidados intensivos. En el seguimiento del tratamiento, se documentaron los problemas de oxígeno con un flujo aéreo inferior a 270 l/min, que se observaron en ausencia de la intervención de la fisioterapia respiratoria, con el uso de un dispositivo de asistencia (Cough Assist, insuflador-exsuflador, M-E, Emerson) y los cuidadores se entrenaron en su uso. Excepción en situaciones de emergencia, la modalidad de ventilación fue establecida después de consulta con el paciente y sus cuidadores. La tolerancia se optimizó en sesiones de entrenamiento. Los pacientes fueron monitoreados de cara a la realización de los procedimientos planificados y llamadas telefónicas, y se observaron en casa por el equipo de atención sanitaria.

En el seguimiento de pacientes hospitalizados, el paciente fue excluido del estudio al día 31 de diciembre de 2010.

El periodo de seguimiento para el paciente incluido en el estudio fue de 14,36-129,6 días (IC 95%: 14,36-129,6). La media de edad de los pacientes fue de 72 meses (IC 95%: 14,36-129,6), la mediana de 49,6 ± 17,5 (IC 95%: 15,3-83,8). Se realizó un análisis estadístico para las diferencias en las características de los pacientes y se determinó la supervivencia en domicilio, la aceptación y la tolerancia fueron aceptables.

Conclusiones: La ventilación mecánica prolonga la supervivencia de la ELA. La evaluación neurológica programada tiene un impacto favorable en la supervivencia de los pacientes con ELA y constituye un elemento esencial en el manejo multidisciplinario de esta enfermedad.

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quantitative variables as mean or median, standard deviation and range. Survival in each of the subgroups was analyzed according to the Kaplan–Meier method. The level of significance for the whole study was set at 0.05. The statistical software package SPSS version 18.0 for Windows was used for data analysis.

### Results

During the study period, 114 patients met the inclusion criteria, 57 (50%) men and 57 (50%) women. Patient age at the time of ALS diagnosis was 67.3±10.8 years (mean±standard deviation), with a range of 30–88 years. Disease onset was predominantly bulbar in 64 (56.2%) of cases and non-bulbar in 50 (43.8%).

Most patients, namely 70 cases (61.4%), were evaluated and monitored by a pulmonologist at some time during the course of their disease, while 44 (38.6%) had no pulmonary consultation nor follow-up. For 12 cases (10.5%), their first contact with the pulmonary medicine department occurred when they were admitted for acute respiratory failure. Nine patients (7.9%) had seen a pulmonologist for other reasons before their ALS diagnosis, two cases being monitored for bilateral phrenic nerve palsy, two for elevated hemidiaphragm, two for sleep apnea–hypopnea, one for tuberculosis sequelae and radiation therapy, one for dyspnea and expectoration of undefined origin, and one for non- obstructive ventilatory changes. Mean time from ALS diagnosis to the first visit to a pulmonologist was 12.17±15.16 months (median 6.34 months).

Table 1 shows the indications for mechanical ventilation. NIV was indicated in 43 of the 114 cases (37.7%). In 11 (25.6%), it was initiated for respiratory failure during hospital admission without prior evaluation by a pulmonologist. Thirty-seven (32.5%) patients continued to receive non-invasive ventilation, while six required subsequent tracheostomy and invasive ventilation. A total of seven patients (6.1%) received invasive ventilation, in one case without having been treated previously with NIV. Mechanical cough assistance was used in 15 cases (13.2%), in one case without simultaneous mechanical ventilation. Pre-ventilation spirometric data were available in 30 of the NIV patients with a percent predicted FVC of 44.1±20.4%. Nocturnal oximetry before starting NIV was performed in 23 patients; mean CT90 was 18.6±31.3%.

By the end of the follow-up period, 106 patients (92.9%) had died. We excluded 2 cases from the survival analysis, since the exact date of death could not be determined. Mean survival of all patients after disease diagnosis was 28.0 months (95% confidence interval [95% CI], 21.1–34.8), and median, 20.0±1.4 months (95% CI, 17.2–22.7).

Mean survival of the 37 patients who received NIV and did not subsequently receive invasive ventilation (20 with predominantly bulbar involvement and 17 non-bulbar) was 23.3 months (95% CI, 16.7–28.8), with a median of 19.7 (95% CI, 14.0–25.4). No significant differences were found in survival between these patients and the 70 cases that did not receive ventilatory support of any kind (38 with bulbar involvement), with a mean survival of 26.7±4.5 months and median 18.9 (95% CI, 15.3–22.6).

Median survival of ALS patients with non-bulbar disease after diagnosis who received NIV was 30.15 months (95% CI, 19.1–41.2), median 24.8±5.4 (95% CI, 14.2–35.3), while in patients with bulbar ALS it was 17.4 months (95% CI, 10.5–24.2), median 13.4±2.4 (95% CI, 8.6–18.1), although the difference was not significant. Survival, when calculated from the start of NIV, was longer in patients without bulbar involvement than in those with, but the difference was not statistically significant (Fig. 1).

![Fig. 1. Survival after ALS diagnosis in patients receiving NIV who did not subsequently receive invasive ventilation: without bulbar involvement (n=17) and with bulbar involvement (n=20).](image-url)

The impact of evaluation by a pulmonologist before ventilatory treatment was analyzed in the 37 patients who received NIV only. In the 26 patients who were prescribed programmed ventilation (13 with bulbar involvement), survival was greater than in the 11 who were prescribed ventilatory support in an emergency situation without prior respiratory evaluation (seven with bulbar involvement). Thus, mean survival, if calculated from the time of ALS diagnosis, was 27.1 months (95% CI, 18.5–35.8) vs 14.0 months (95% CI, 9.1–18.9), P<.012 (Fig. 2), or, from the time of starting ventilation, 12.3 months (95% CI, 5.8–18.7) vs 2.8 months (95% CI, 0.6–5.0), P<.004 (Fig. 3). In patients with prior evaluation by a pulmonologist, time from diagnosis to start of ventilation was 18.7±16.4 months, while in the other group of patients it was 11.5±10.3 months, a difference that was not statistically significant. There were no differences in age, sex and bulbar involvement between the two groups.

With regard to invasive ventilation, mean survival since diagnosis in the seven patients who received invasive ventilation was 72 months (95% CI, 14.36–129.6), median 49.6±17.5 months (95% CI, 15.3–83.8). This was significantly greater than in the 107 patients who did not receive invasive treatment (P<.01). Of these seven patients, two died within a year after starting invasive ventilation.

### Table 1

<table>
<thead>
<tr>
<th>Type of Ventilatory Support</th>
<th>NIV</th>
<th>Invasive ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases and ventilatory modes (5% of 114)</td>
<td>43 (37.7)</td>
<td>7 (6.1)</td>
</tr>
<tr>
<td>NIV throughout study follow-up</td>
<td>37</td>
<td>–</td>
</tr>
<tr>
<td>Started NIV then switched</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>to invasive ventilation</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Started invasive ventilation directly without prior NIV Bulbar involvement</td>
<td>26</td>
<td>6</td>
</tr>
</tbody>
</table>

Interval between diagnosis and start of ventilation

<table>
<thead>
<tr>
<th>Mean±SD (months)</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.7±17.0</td>
<td>12.7</td>
</tr>
<tr>
<td>28.8±31.0</td>
<td>20.1</td>
</tr>
</tbody>
</table>

NIV: non-invasive ventilation; SD: standard deviation.
Discussion

Clinical characteristics of ALS are progressive, severe and incurable paralysis of the voluntary muscles due to destruction of motor neurons. Patients become dependent for activities of daily living, and when the disease affects the ventilatory muscles, respiratory failure occurs, generally leading to death. No treatment is known to effectively halt the deadly progress of this disease, so when respiratory failure develops, the only recourse is mechanical ventilation.7

In recent years, user-friendly, non-invasive pressure ventilators have become available and have contributed significantly to the management of these patients. These ventilators are not only effective, they are also very well tolerated and are now used both in the hospital and in the home. The efficacy of NIV in ALS is supported by the studies evaluated in two recent systematic reviews, and their impact on quality of life is favorable.12,13 One of the most significant of these studies is that of Bourke et al.,14 due to its randomized and controlled design. These authors randomized 22 patients to NIV and 19 to standard care without mechanical ventilation, and found that in patients without severe bulbar dysfunction, NIV increased survival by 205 days with improved quality of life measured by generic ALS-specific instruments. In patients with severe bulbar involvement, NIV did not increase survival but it did help improve some aspects of quality of life, such as symptoms derived from sleep changes.15 In our study, we found a trend toward improved survival in non-bulbar patients, whose mean survival after NIV was 12.9 months vs 6 months in bulbar patients. This difference was not statistically significant, probably due to the small sample size and the lack of homogeneity between the groups in terms of severity and time since diagnosis. Although survival in patients who only received NIV was not statistically different from that of non-ventilated patients, it is important to bear in mind that in addition to the difference in sample size, these cases had greater respiratory involvement at the time of diagnosis.

Programmed consultation with the pulmonologist, with evaluation of clinical status and respiratory function in patients with suspected or diagnosed ALS, allows the early identification of patients who may respond to NIV.15 The practice in our hospital is probably typical of the standard practice in other similar general hospitals: during the study period we did not have a dedicated ALS unit, and only 43% of patients were referred for a programmed visit with the pulmonologist. Moreover, the 12 most severe cases admitted due to respiratory failure had had no prior respiratory evaluation. It is interesting to note that in nine patients who presented with atypical symptoms, the diagnosis of ALS was made in the pulmonology outpatient clinic, underscoring the fact that this disease can be found in standard respiratory practice.

In our series, referral to the pulmonologist was reflected in health outcomes. Excluding the more severe cases that required invasive ventilation, all patients that were treated with NIV only and were seen for a programmed evaluation before mechanical ventilation was indicated had better survival. This outcome is even better if survival is evaluated from the start of NIV. These results are in line with those of Farrero et al.15

If respiratory deficit is severe and NIV is ineffective, the alternative is invasive ventilation. This decision must only be taken after conferring with the patient and caregivers, and if it is rejected, palliative pharmacological sedation may be offered. These factors explain why only six patients with bulbar involvement went on to invasive ventilation after receiving NIV. Invasive ventilation does not halt disease progression, but it can be used safely in the home, can prolong survival, and is reasonably well tolerated. Sanchez et al.16 reported that 78.8% of their patients were still alive one year after starting invasive ventilation. Although our case series is smaller, our experience is similar, with only 2 of the 7 patients dying
within 1 year of starting this treatment. Their survival was greater than that of any of our other patients, although the non-invasive ventilation group varied greatly in clinical presentation and severity, and invasive ventilation was refused in some severe cases. In all, survival on invasive ventilation in these cases must be associated with the overall care received by the patient and with the lack of significant complications associated with the tracheostomy, as reported elsewhere.17

In addition to its retrospective nature, this study has other limitations. Patient management was not homogeneous over the long study period, and in the initial years fewer referrals for respiratory evaluation were made. Quality of life was not assessed, sleep studies were not routine, and no real data are available on compliance (although this improved). Patients with admission records were included, but patients who were not hospitalized during the study period were not. The latter are usually patients with less initial respiratory involvement or good family and social welfare support. In contrast, patients who were hospitalized were admitted for severe respiratory failure, adjustment of ventilation parameters, percutaneous endoscopic gastrostomy (PEG) placement, complex tests, or social reasons. Nevertheless, after a 10-year study period, the sample can be said to represent the status quo in our hospital, and in our opinion, is a good reflection of the care practices in a hospital without a dedicated ALS unit.

ALS is a complex disease that is difficult to diagnose; the disease course is complicated, and patients are highly dependent on medical care.1 Protocolized respiratory evaluation and monitoring by pulmonologists prolong survival and improve quality of life. However other needs must also be addressed, such as PEG feeding,18 the use of specialized technology for mobility and communication,19 palliative sedation, and the psychological support and care of patients, caregivers and family.9 This multi-faceted situation can only be effectively dealt with by a multidisciplinary team of professionals willing to share their decisions with patients and caregivers.20

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Conflict of Interests

The authors state that they do not have any conflict of interests associated with this study.

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