Slower Disease Progression and Prolonged Survival in Contemporary Patients With Amyotrophic Lateral Sclerosis

Is the Natural History of Amyotrophic Lateral Sclerosis Changing?

Adam Czaplinski, MD; Albert A. Yen, MD; Ericka P. Simpson, MD; Stanley H. Appel, MD

Background: In recent years, considerable effort has been made to improve the treatment of patients with amyotrophic lateral sclerosis (ALS). However, despite the increased use of supportive measures, controversy still exists about overall trends in disease progression and survival.

Objective: To analyze whether survival and disease progression in patients with ALS have changed during the past 20 years.

Design: By using the Kaplan-Meier life-table method, we compared disease progression (measured as time to a 20-point increase in the Appel ALS score) and survival in 1041 patients diagnosed as having ALS between January 1, 1984, and January 1, 1999 (historical group, n=647), and between January 2, 1999, and November 1, 2004 (contemporary group, n=394). The Cox proportional hazards model was used for univariate and multivariate analyses.

Results: The median survival from symptom onset was 4.32 years (95% confidence interval [CI], 3.81-4.84 years) in the contemporary group compared with 3.22 years (95% CI, 3.04-3.41 years) in the historical group (P<.001). The contemporary patients progressed more slowly (10 months to a 20-point increase; 95% CI, 9-13 months) compared with patients in the historical group (9 months to a 20-point increase; 95% CI, 8-9 months) (P<.001). In the multivariate Cox proportional hazards model, the observed outcome improvement over time was independent of confounding factors, such as age, sex, diagnostic delay, site of symptom onset, baseline forced vital capacity, and baseline Appel ALS score, and independent of the use of potentially outcome-modifying therapies (riluzole, noninvasive ventilation, and percutaneous gastrostomy).

Conclusions: Contemporary patients had significantly prolonged survival and slower disease progression compared with patients from the historical group. The improved outcome seemed independent of specific ALS outcome-modifying therapies, but we cannot rule out an effect of comorbid conditions, which could have influenced medical treatment and survival. Nevertheless, our observations suggest the possibility that disease course has changed and that ALS is becoming less aggressive over time. Further studies are needed to determine whether there has been a fundamental change in the natural history of the disease or whether our results are because of other unmeasured aspects of improved multidisciplinary care.

Arch Neurol. 2006;63:1139-1143
In a prior publication,13 506 patients were monitored for sur-
gastrostomy.
FVC, forced vital capacity; NIV, noninvasive ventilation; PEG, percutaneous
trace, a recent report9 provides contradictory data show-
after controlling for potential confounding variables. In con-
care.
was associated with improvement in the standard of
mal treatment of patients with ALS.10,11 A recent re-
American Academy of Neurology and the World Fed-
We used this particular cutoff because in 1999 the
temporary group (January 2, 1999–November 1, 2004).
was divided into 2 groups: first examination (FE) between January 1, 1984, and

Table 1. Demographic and Clinical Characteristics
of the 2 Groups*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1984-1999</th>
<th>1999-2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>647</td>
<td>394</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>68.0</td>
<td>64.0</td>
</tr>
<tr>
<td>Female</td>
<td>32.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Age at onset, y†</td>
<td>53.59 (13.04)</td>
<td>55.11 (13.56)</td>
</tr>
<tr>
<td>Site of initial symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar muscles</td>
<td>20.1</td>
<td>10.7</td>
</tr>
<tr>
<td>Limbs</td>
<td>19.9</td>
<td>89.3</td>
</tr>
<tr>
<td>Diagnostic delay, mo‡</td>
<td>12.99 (9.25)</td>
<td>14.21 (15.95)</td>
</tr>
<tr>
<td>AALSS†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62.71 (18.52)</td>
<td>64.26 (19.58)</td>
</tr>
<tr>
<td>Preslope</td>
<td>2.76 (1.98)</td>
<td>2.55 (2.02)</td>
</tr>
<tr>
<td>Baseline FVC†</td>
<td>81.60 (20.94)</td>
<td>85.11 (20.90)</td>
</tr>
<tr>
<td>Riluzole use ever</td>
<td>23.0</td>
<td>72.1</td>
</tr>
<tr>
<td>NIV yes</td>
<td>8.4</td>
<td>18.8</td>
</tr>
<tr>
<td>PEG yes</td>
<td>33.8</td>
<td>14.5</td>
</tr>
</tbody>
</table>

Abbreviations: AALSS, Appel amyotrophic lateral sclerosis score; FVC, forced vital capacity; NIV, noninvasive ventilation; PEG, percutaneous
*Data are given as percentage of each group unless otherwise indicated.
†Data are given as mean (SD).
‡Data are given as median (SD).

between 1994 and 1998.8 This effect remained significant, even after controlling for potential confounding variables. In contrast, a recent report7 provides contradictory data showing a significant increase in survival in 793 Italian patients with ALS observed over 28 years.

In the present study, we investigated whether survival and disease progression in patients with ALS have changed during the past 20 years by stratifying our ALS database population into 2 groups according to the date of first examination and the date of diagnosis: a historical group (January 1, 1984–January 1, 1999) and a contemporary group (January 2, 1999–November 1, 2004). We used this particular cutoff because in 1999 the American Academy of Neurology and the World Federation of Neurology published guidelines for the optimal treatment of patients with ALS.10,11 A recent report12 suggests that the publication of these guidelines was associated with improvement in the standard of care.

METHODS

In a prior publication,11 506 patients were monitored for survival and 321 for disease progression. Since then, we have been more successful in observing a larger percentage of patients diagnosed by us as having ALS. Thus, in the present study, we examined data on 1041 patients diagnosed as having definite or probable ALS14; these patients were observed at our ALS clinic for more than 20 years. We have no evidence that the patients being observed in the clinic have less aggressive disease than those not being observed.

Two outcome measures were used in this study: survival and time to 20-point progression in Appel ALS score (AALSS). Survival was defined as the number of months from symptom onset until death from any cause or tracheotomy. Patients who remained alive without tracheotomy were censored at the last known follow-up. First symptoms were confirmed by the family or other observers, whenever possible. As an alternative way to view disease progression as a mean rate of change in the given score or the score change from baseline to the study end point, we considered time to 20-point increase in total AALSS from baseline examination as an index of disease progression. Time to 20-point increase in AALSS was determined from patient examination scores. If a patient never exceeded a 20-point increase in AALSS during the study period, the patient was considered censored at the latest examination date. A 20-point change was chosen because it is indicative of a clinically evident change in a patient’s clinical status and ability to perform activities of daily living.13

Statistical analyses were performed using a commercially available software program (SPSS, version 11.5.1; SPSS Inc, Chicago, Ill). Outcome analyses were performed using the Kaplan-Meier life-table method. The log-rank test was used to assess equality of outcome functions. The Cox proportional hazards model was used for univariate and multivariate analysis. The hazard ratio was calculated for each variable. P<.05 was considered statistically significant.

RESULTS

Of the analyzed 1041 patients, 394 (37.8%) were first examined in our clinic between 1999 and 2004 and 647 (62.2%) between 1984 and 1999. Notably, there were several differences between both groups in terms of distribution of potentially outcome-influencing factors. The contemporary group was characterized by a lower percentage of patients whose disease was termed bulbar onset. In addition, more patients in this group received riluzole and underwent NIV therapy. On the other hand, the patients in the historical group were younger, had a lower AALSS at baseline, and underwent PEG therapy more often (Table 1).

The median survival from symptom onset was 4.32 years (95% confidence interval [CI], 3.81–4.84 years) in the 1999 to 2004 group compared with 3.22 years (95% CI, 3.04–3.41 years) in the 1984 to 1999 group (P<.001) (Figure 1).
The conditions of patients diagnosed as having ALS more recently progressed slower (10 months to a 20-point progression; 95% CI, 9-13 months) compared with the patients diagnosed as having ALS between 1984 and 1999 (9 months to a 20-point progression; 95% CI, 8-9 months) (P < .001) (Figure 2).

When the effect of the time of diagnosis (as categorical variable first examination before vs after 1999) on outcome was analyzed using univariate Cox proportional hazards analysis, contemporary patients had a reduced risk of death, and a reduced risk of 20-point AALSS progression compared with patients diagnosed as having ALS in the earlier period (Table 2). Moreover, if the hazard ratio and 95% CI were adjusted for age, sex, and site of symptom onset (model 1), being diagnosed as having ALS between 1999 and 2004 remained significantly associated with longer survival and slower disease progression (Table 2).

Most important, because of differences between the analyzed groups in demographic and clinical characteristics (age and bulbar onset) and in the use of the potentially outcome-modifying therapies (NIV, PEG, and riluzole), we investigated whether the observed outcome improvement over time is dependent on these factors. We used a multivariate Cox proportional hazards regression model (model 2) and analyzed all potentially relevant covariates, such as age, sex, site of onset, diagnostic delay, baseline forced vital capacity, baseline AALSS, AALSS preslope (rate of change between first symptom and first examination), and riluzole, NIV, and PEG use. In most patients who received riluzole, therapy was initiated at the first examination and at diagnosis, before a documented 20-point progression. In contrast, NIV and PEG are generally indicated in later stages of disease, far beyond the initial progression of 20 points. Thus, in setting up the Cox proportional hazards model for disease progression, we did not include NIV and PEG use. In this final multivariate model, the time of first examination (as categorical variable first examination before vs after 1999) was confirmed as a significant and independent covariate of disease progression and survival in our patient population (Table 3 and Table 4, respectively).

We have used our database to determine whether survival and disease progression in patients with ALS have changed during the past 20 years. We found that contemporary patients, observed in our clinic between 1999 and 2004, had prolonged survival and slower disease progression compared with patients from 1984 to 1999. However, there were differences between the analyzed groups in several demographic and clinical features, and in the use of therapies. The growing numbers of patients treated with riluzole or undergoing NIV therapy in the contemporary group were not unexpected and are in agreement with previous reports. However, the difference in the percentage of patients with bulbar symptoms requires explanation. It is clear that no data indicate decreased numbers of patients with bulbar disease onset between the contemporary and historical groups. The most likely explanation would be a change in assigning patients to the group with bulbar symptom onset in 1999 to 2004 compared with 1984 to 1999. From 1984 to 1999, we assigned patients to the bulbar-onset

---

**Table 2. Univariate and Multivariate Analyses of the Effect of the Time of the First Examination (Before vs After 1999) on Survival and Disease Progression**

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>1984-1999</th>
<th>1999-2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted data</td>
<td>1.00</td>
<td>0.73</td>
</tr>
<tr>
<td>Model 1 adjusted</td>
<td>1.00</td>
<td>0.69</td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted data</td>
<td>1.00</td>
<td>0.69</td>
</tr>
<tr>
<td>Model 1 adjusted</td>
<td>1.00</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Data are given as hazard ratio (95% confidence interval). P < .001 for the difference between the 2 periods for all analyses.

†Adjusted for age, sex, and site of onset.

**Table 3. Multivariate Analysis of the Time to 20-Point AALSS Progression**

<table>
<thead>
<tr>
<th>Category</th>
<th>HR (95% CI) for Model 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>1.01 (1.00-1.02)</td>
<td>.005</td>
</tr>
<tr>
<td>Limb vs bulbar onset</td>
<td>1.37 (1.01-1.72)</td>
<td>.006</td>
</tr>
<tr>
<td>FS-FE time (months)</td>
<td>0.99 (0.98-1.00)</td>
<td>.04</td>
</tr>
<tr>
<td>First AALSS</td>
<td>1.02 (1.01-1.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AALSS preslope</td>
<td>1.23 (1.14-1.32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FE 1984-1999 vs FE 1999-2004</td>
<td>0.73 (0.60-0.89)</td>
<td>.002</td>
</tr>
<tr>
<td>Male vs female</td>
<td>0.97 (0.82-1.03)</td>
<td>.60</td>
</tr>
<tr>
<td>First FVC</td>
<td>1.00 (0.99-1.00)</td>
<td>.90</td>
</tr>
<tr>
<td>Riluzole use (ever vs never)</td>
<td>1.03 (0.85-1.23)</td>
<td>.80</td>
</tr>
</tbody>
</table>

Abbreviations: AALSS, Appel amyotrophic lateral sclerosis score; CI, confidence interval; FE, first examination; FS, first symptom; FVC, forced vital capacity; HR, hazard ratio.

*Model 2 was used: all factors were analyzed in the same Cox proportional hazards model.
group when bulbar symptoms were thought to predomi-
nate the clinical picture at diagnosis (“primarily” bul-
bar). In contrast, in the more recent period (1999-
2004), only patients whose initial symptoms were bulbar
(“primary” bulbar) were assigned to the bulbar-onset

Despite the differences in terms of clinical character-
istics and therapy use between groups, the outcome ben-
efit remained significant in univariate and multivariate
analyses after correcting for these potential confound-
ing factors.

Our final statistical model also suggests that the im-
proved outcome in contemporary patients is indepen-
dent of riluzole use and of the use of PEG and NIV. How-
ever, while we did not find a significant effect of riluzole
therapy in our patient population, the use of PEG and
NIV (ever vs never) was clearly a marker of advanced dis-
ease, which may suggest that these interventions were
probably performed late in the disease course in se-
verely impaired patients. These findings are consistent
with those of some previous reports from clinical trials
and database cohorts. In addition, when assessing the po-
tential impact of PEG or NIV use, our database allowed
an ever vs never analysis only and was not sufficient to
analyze the timing of the therapeutic interventions (ie,
performing survival analyses from the point of PEG or
NIV initiation) and to address the compliance issue for
those therapies. This is a relevant weakness of our study,
which makes it difficult to definitely address the effect
of these potentially disease-modifying therapeutic inter-
ventions on the observed improvement in outcome.

During the 20-year observation period, different di-
agnostic criteria were used. However, in our experi-
ence, the diagnostic and clinical features of patients di-
agnosed as having definite or probable ALS after 1994.14
In addition, our database did not allow the inclusion of
patients with possible or suspected ALS into the analy-
sis. This selectivity in patients may be viewed as another
limitation of our study.

Although the prolonged survival and slower disease
progression during the past years could be viewed as an
effect of patients being seen in a multidisciplinary clinic,
our patients have been observed in the same multidisci-


tary clinic since 1984. Furthermore, the improve-
ment in survival and progression is not just a recent
phenomenon during the past 5 years; improvement has
been ongoing during the past 20 years.17 It is certainly
possible that improvements in medical treatment and
survival from comorbid conditions could have contrib-
ted to the positive effects observed in the contemporary
cohort. Nevertheless, the improved outcomes also sug-
gest the possibility that the natural history of ALS is
changing, with the disease becoming less aggressive.
Clearly, further studies are required to test the validity
of this hypothesis.


table 4. multivariate analysis of survival*

<table>
<thead>
<tr>
<th>Category</th>
<th>HR (95% CI) for Model 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>1.04 (0.96-1.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male vs female</td>
<td>0.76 (0.62-0.92)</td>
<td>.005</td>
</tr>
<tr>
<td>FS-FE time (months)</td>
<td>0.97 (0.96-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First FVC</td>
<td>0.99 (0.98-0.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AALSS preslope</td>
<td>1.29 (1.20-1.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FE 1984-1999 vs FE 1999-2004</td>
<td>0.47 (0.30-0.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PEG use (ever vs never)</td>
<td>0.75 (0.63-0.90)</td>
<td>.003</td>
</tr>
<tr>
<td>NIV use (ever vs never)</td>
<td>0.41 (0.27-0.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Limb vs bulbar onset</td>
<td>1.07 (0.85-1.34)</td>
<td>.50</td>
</tr>
<tr>
<td>First AALSS</td>
<td>1.00 (0.99-1.01)</td>
<td>.80</td>
</tr>
<tr>
<td>Riluzole (ever vs never)</td>
<td>1.17 (0.97-1.43)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: AALSS, Appel amyotrophic lateral sclerosis score; CI, confidence interval; FE, first examination; FS, first symptom; FVC, forced vital capacity; HR, hazard ratio; NIV, noninvasive ventilation; PEG, percutaneous gastrostomy.

*Model 2 was used: all factors were analyzed in the same Cox proportional hazards model.

Accepted for Publication: February 27, 2006.
Correspondence: Stanley H. Appel, MD, Department of Neurology, Methodist Neurological Institute, 6550 Fannin, Suite 802, Houston, TX 77030 (SAppel@tmh.tmc.edu).

Author Contributions: Study concept and design: Czapinski, Yen, Simpson, and Appel. Acquisition of data: Czapinski and Simpson. Analysis and interpretation of data: Czapinski and Yen. Drafting of the manuscript: Czapinski and Yen. Critical revision of the manuscript for important intellectual content: Czapinski, Yen, Simpson, and Appel. Statistical analysis: Czapinski and Yen. Obtained funding: Appel and Czapinski. Administrative, technical, and material support: Czapinski. Study supervision: Appel.

Funding/Support: This study was supported by the Muscular Dystrophy Association, the Houston Endowment, the Swiss National Science Foundation (Dr Czapinski), and Fonds zur Foerderung des Akademischen Nachwuchses, University of Basel (Dr Czapinski). Dr Czapinski was the recipient of the Sheila Essey ALS Fellowship Award.

Acknowledgments: We thank Joan Appel, the ALS clinical research coordinator, our patients with ALS, and the MDA/ALS Center team at Methodist Neurological Institute and Baylor College of Medicine for their contributions to the database; and Andreas Schoetzau, Dipl-Math, for his statistical advice and comments.

REFERENCES

1. Bensimon G, Lacambllez L, Meinering V; ALS/Riluzole Study Group. A con-
330:585-591.

2. Lacambllez L, Bensimon G, Leigh PN, Guillet P, Meinering V; Amyotrophic Lat-
eral Sclerosis/Riluzole Study Group II. Dose-ranging study of riluzole in amy-

3. Chio A, Finocchiaro E, Meiner V, Bottacchi E, Schiffer D; ALS/Percutaneous En-
deroscopic Gastrostomy Study Group. Safety and factors related to survival after

4. Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ. Noninvasive ventilation in

©2006 American Medical Association. All rights reserved.

Downloaded From: http://archneur.jamanetwork.com/pdfaccess.ashx?url=/data/journals/neur/7067/ on 06/26/2017


Announcement

Visit www.archneurol.com. As an individual subscriber you can send an e-mail to a friend. You may send an e-mail to a friend that includes a link to an article and a note if you wish. Links will go to free abstracts whenever possible.