Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors

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Abstract

We performed a historical cohort study of 307 untreated patients with probable or definite amyotrophic lateral sclerosis in order to investigate whether the mortality risk changed during the disease course and to identify prognostic factors at diagnosis. Patients were diagnosed in one of the academic hospitals in The Netherlands and followed-up for at least 6 years after diagnosis. The median survival from diagnosis was 1.4 years (95% confidence interval, 1.3–1.6 years) with an estimated 5- and 10-year survival of 20 and 8%, respectively. Mortality was at its maximum in the second year after diagnosis and declined considerably thereafter. Observed mortality approached the expected mortality in patients who survived diagnosis 6 or more years. In univariate and multivariate analyses, young age, limb onset, and a long delay between initial weakness and diagnosis were associated with lower mortality. The better prognosis of limb-onset patients was not observed in females. Patients with initial respiratory muscle weakness, had the worst prognosis with a median survival of only 2 months. The significantly greater mortality of older patients proved not to result from a rise in expected mortality only. In conclusion, the annual mortality risk in ALS does not remain constant throughout the disease and depends on age at diagnosis, site of onset, diagnostic delay, but also on the time since diagnosis. These findings may have consequences for the planning of symptomatic care and the design and analysis of therapeutic trials.   © 1997 Elsevier Science B.V.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of the upper and lower motor neurons (Leigh and Ray-Chaudhuri, 1994). It leads to progressive weakness and severe disability within a few years. The diagnosis usually carries a poor prognosis with a median survival of 1–3 years from diagnosis (Christensen et al., 1990; Norris et al., 1993) and of 2–4 years from initial weakness (Tysnes et al., 1991; Chancellor et al., 1993; Eisen et al., 1993; Haverkamp et al., 1995). The course of the disease is reported to be slowly progressive with a linear decline of muscle strength (Munsat et al., 1988) and a constant risk of death (Christensen et al., 1990; Norris et al., 1993). This is at odds with clinical experience that a substantial proportion of patients survive diagnosis 5 or more years (Mulder and Howard, 1976; Christensen et al., 1990; Norris et al., 1993) and that these patients seems to have a better prognosis than those who have been diagnosed more recently. Furthermore, survival is known to vary considerably and is considered to be difficult to predict in individual cases, but how and why patients differ is not yet clear. Clinical characteristics related to survival

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probably include age (Juergens et al., 1980; Uebayashi et al., 1983; Kondo and Hemmi, 1984; Caroscio et al., 1987; Jablecki et al., 1989; Christensen et al., 1990; Chancellor et al., 1993; Eisen et al., 1993; Norris et al., 1993; Haverkamp et al., 1995) and site of onset (Mulder and Howard, 1976; Uebayashi et al., 1983; Kondo and Hemmi, 1984; Mortara et al., 1984; Caroscio et al., 1987; Christensen et al., 1990; Chancellor et al., 1993; Norris et al., 1993).

In order to study the mortality risk throughout the disease and identify prognostic factors related to mortality, we performed a historical cohort study of untreated patients with ALS, who were referred to one of the university hospitals in The Netherlands.

2. Materials and methods

2.1. Patients

We retrieved the hospital records of consecutive patients who had been diagnosed as having ALS or motor neuron disease between January 1, 1970 and January 1, 1988. All available clinical data were reviewed for confirmation of the diagnosis. Patients who fulfilled the clinical diagnostic criteria for probable or definite ALS (Brooks, 1994) were eligible for the study: upper and lower motor neuron signs; insidious onset and progression of weakness; involvement of at least two body regions (bulbar, cervical, thoracic, lumbosacral) in patients with probable ALS and at least three regions in those with definite ALS; no signs or symptoms outside the motor system; and no other neurological or systemic disorders likely to mimic the clinical syndrome (Louwerse et al., 1991; Brooks, 1994; Leigh and Ray-Chaudhuri, 1994).

2.2. Follow-up

Patients were followed-up for at least 6 years after diagnosis. The primary endpoints were death from any cause or chronic assisted ventilation. We obtained information on the date and cause of death from the medical records, autopsy reports, neurologists or general practitioners. Moreover, death was confirmed by the government register.

2.3. Data analysis

We estimated survival from the date of diagnosis using life-table methods (Kaplan and Meier, 1958). The survival times of patients alive on January 1, 1994, were considered to be censored. Survival of patients unavailable for follow-up contributed to the estimated survival until the date of their last follow-up visit. We imputed missing dates of diagnosis by adding the median delay between the first neurological consultation and diagnosis to the date of first

consultation, adjusted for age and site of onset (Beck, 1988).

The annual observed mortality in the study cohort was compared with the usually expected mortality. The expected mortality was based on mortality rates obtained from Dutch vital statistics, matched for age, sex, and calender period (Verheul et al., 1993). Disease-specific excess mortality was calculated by subtracting the expected mortality from the observed mortality.

Patient characteristics subjected to univariate and multivariate analyses were sex, age at diagnosis, site of onset, delay from initial weakness to diagnosis, familial or sporadic type of ALS, and clinical features at diagnosis. The date of initial weakness was taken as the onset of the disease recognizing that fasciculations, fatigue and muscle cramps often preceded weakness and may have been the first symptoms. The date of diagnosis was the date all initial investigations were completed and other disorders resembling ALS were excluded. Patients whose first symptoms were dysarthria or dysphagia, were considered to have bulbar-onset ALS.

The prognostic value of each specific factor was expressed in terms of hazard ratio, which may be interpreted as a relative risk. The hazard ratio represents the mortality risk per interval of time in the presence of a specific factor, relative to the risk in the absence of this factor. Crude hazard ratios were estimated by univariate analyses and adjusted hazard ratios by multivariate analyses using the proportional hazards regression model to correct for simultaneously effective covariables (Cox, 1972). All analyses were performed using the SAS Statistical Packages (SAS Institute, 1988).

3. Results

3.1. Patients

The study cohort consisted of 307 patients, 170 males and 137 females. We excluded 173 patients, coded under the diagnostic category of ALS or motor neuron disease, but who did not fulfil the clinical diagnostic criteria of probable or definite ALS, including 47 patients with progressive spinal muscular atrophy, one with progressive bulbar palsy, 16 with primary lateral sclerosis, 20 with multisystem atrophy, one with a suspected post-poliomyelitis syndrome, 17 with ALS-mimic syndromes (Louwerse et al., 1991; Brooks, 1994; Leigh and Ray-Chaudhuri, 1994), and 71 with various revised diagnoses, amongst others peripheral neuropathy, spinal cord or brainstem compression, multiple sclerosis, myopathy, and stroke. In addition, we excluded 11 patients, because they were lost to follow-up, and 58 because of uncertainty about both the date of diagnosis and first neurological consultation. Finally, we excluded 30 patients who were or had been treated with experimental drugs.

Table 1
Patient characteristic at diagnosis

Characteristics	
Number of patients	307
Sex (%)	
Female	137 (45)
Male	170 (55)
Mean age, years (±SD)	
At onset	60 (12)
At diagnosis	61 (12)
Site of initial weakness (%)	
Bulbar muscles	88 (29)
Limbs	184 (60)
Respiratory muscles	4 (1)
Mixed	31 (10)
Median diagnostic delay, months (95% CI)	
From initial weakness	10 (9–11)
From neurological consultation	2 (1–3)
Heredity (%)	
Sporadic ALS	287 (93)
Familial ALS	20 (7)

Values are numbers (%), means (±SD), or medians (95% CI). SD, standard deviation; CI, confidence interval.

The patient characteristics are shown in Table 1. The sex ratio differed in the various clinical variants of ALS, with a female excess in the group presenting with bulbar symptoms and a male preponderance in patients below the age of 40. Half of the patients were diagnosed between 56 and 68 years of age. Females were older at diagnosis than males, bulbar-onset patients older than those presenting with limb weakness, and sporadic cases older than familial cases, whereas age at diagnosis did not differ significantly between those with onset in the upper and lower limbs. Most frequently, patients had their initial symptoms in the limb muscles with weakness of the upper (77 patients; 25%) or lower limbs (107 patients; 35%). In 31 patients (10%), first weakness occurred simultaneously in bulbar and limb muscles. The median delay between initial weakness and ultimate diagnosis was 10 months; it was shorter for patients with bulbar onset, but did not depend on age or sex. The long delay was mainly caused by the patient himself: following the first neurological consultation, a median period of only 2 months elapsed before the ultimate diagnosis was made. In most patients, the disease was far advanced at the time of diagnosis; 215 patients (70%) had weakness of the upper limbs, 189 (61%) of the lower limbs, 166 (54%) had dysarthria, and 136 (44%) dysphagia.

3.2. Follow-up

Follow-up accumulated 938 patient years. At the completion of the study, 267 (87%) patients had died and 40 (13%) were still alive. In most patients, death resulted from ventilatory muscle weakness, with or without pneumonia. None of the patients received long-term assisted ventilation. Survival varied considerably between individual patients and ranged from 7 days up to 23 years. The median survival from diagnosis was 1.4 years (95% confidence interval, 1.3–1.6 years). Sixty patients (20%) survived diagnosis more than 5 years and 24 patients (8%) more than 10 years. Calculated from the date of initial weakness, median survival was 2.5 years (95% confidence interval, 2.2–2.9 years) with an estimated 5- and 10-year survival of 25 and 15%, respectively.

3.3. Annual mortality risk (Fig. 1)

The annual observed, expected, and excess mortality throughout the disease is shown in Fig. 1. In the first 5 years after diagnosis, mortality was mainly caused by disease-specific excess mortality. The mortality risk was at its maximum in the second year after diagnosis (41% of population per year) and declined considerably thereafter. Six or more years after diagnosis, the disease-specific excess mortality approached the expected mortality.

In the various subgroups of patients, similar annual mortality rates were observed, except for patients aged 40 or younger, in whom the highest mortality occurred in the fourth and fifth year after diagnosis. The greater mortality of older patients was caused by a rise in excess mortality rather than by an increased expected mortality, since the latter did not exceed 6% of population per year even at advanced age.
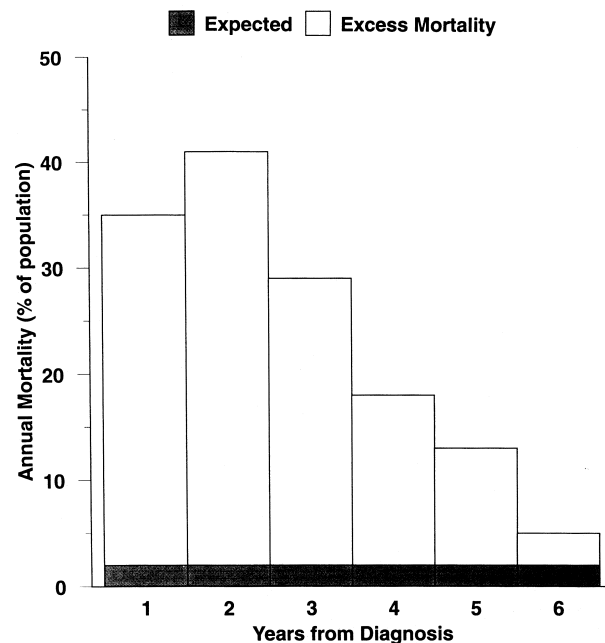

Fig. 1. Annual mortality risk by disease duration since diagnosis in 307 patients with amyotrophic lateral sclerosis. The observed annual mortality is divided into expected mortality and disease-specific excess mortality. Mortality is expressed as a percentage of patient population dying per year.

Table 2
Prognostic factors at diagnosis in amyotrophic lateral sclerosis

	Median survival from diagnosis (95% CI)	Univariate hazard ratio (95% CI) (years)	Multivariate hazard ratio (95% CI)
Sex			
Female	1.3 (1.1–1.5)	1.0	1.0
Male	1.5 (1.3–2.0)	0.7 (0.6–0.9)	—[a]
Age at diagnosis			
>60 years	1.1 (1.0–1.3)	1.0	1.0
40–60 years	2.2 (1.5–2.8)	0.6 (0.4–0.7)	0.6 (0.4–0.8)
≤40 years	5.0 (3.9–[b])	0.2 (0.1–0.4)	0.2 (0.1–0.5)
Site of initial weakness			
Bulbar	1.3 (1.0–1.5)	1.0	1.0
Limbs	1.7 (1.3–2.1)	0.7 (0.4–0.8)	0.6 (0.5–0.8)[c]
Respiratory	0.2 (0.02–1.3)	3.9 (1.4–10.7)	3.7 (1.3–10.3)
Mixed	1.0 (0.7–2.2)	0.9 (0.6–1.4)	—[a]
Time from onset to diagnosis			
≤1 year	1.3 (1.1–1.5)	1.0	1.0
>1 year	1.8 (1.3–2.5)	0.6 (0.5–0.8)	0.7 (0.6–0.9)
Heredity			
Sporadic	1.4 (1.2–1.5)	1.0	1.0
Familial	1.8 (1.4–9.8)	0.6 (0.4–1.0)	—[a]

CI, confidence interval; hazard ratio of the reference group=1.0.
[a]Prognostic factor is eliminated in multivariate analyses.
[b]Too few patients available for reliable estimate of survival.
[c]Prognostic factor for males only.

3.4. Prognostic factors (Table 2, Fig. 2)

The results of univariate and multivariate analyses are listed in Table 2. Univariate analyses indicated that female sex, advanced age, initial weakness in bulbar or respiratory muscles, and sporadic type of the disease were associated with shorter survival times. Multivariate analyses eliminated sex and heredity as independent risk factors. The relatively better prognosis of males was explained by earlier and less frequently bulbar onset. The longer survival of familial cases resulted mainly from a relatively younger age.

3.4.1. Age (Fig. 2b)

Age was the most powerful predictor of survival. Prognosis gradually worsened with advancing age: patients who were diagnosed at an age of 40 or younger had a median survival of 5.0 years, compared with 1.1 year in patients above the age of 60.

3.4.2. Site of onset (Fig. 2c)

Patients who first had bulbar symptoms tended to die earlier than limb-onset patients. None of the bulbar onset cases survived diagnosis more than 6 years. In multivariate analyses, limb onset was a predictor of survival in males only. Patients with onset of weakness in the upper and lower limbs shared an about equal prognosis. Survival of patients with initial weakness in more than one site was comparable with that of bulbar-onset patients. Patients with initial weakness in respiratory muscles without limb or bulbar symptoms, had the worst prognosis with a median survival of only 2 months from diagnosis (95%

confidence interval, 7 days to 16 months). The 24 patients (8%) who survived diagnosis 10 or more years, were all males, who presented with limb weakness and were diagnosed below the age of 40.

3.4.3. Diagnostic delay (Fig. 2d)

Patients who were diagnosed within 1 year after onset of weakness, had a shorter survival than patients in whom diagnosis took longer. This phenomenon was partly caused by other risk factors, especially bulbar onset that shortened both, the time between initial weakness and diagnosis and survival after diagnosis. However, the predictive value remained present after correcting for these variables in multivariate analysis.

3.4.4. Clinical features at diagnosis

In univariate and multivariate analyses, some clinical features, if present at diagnosis, were associated with poor prognosis: dysarthria or dysphagia (adjusted hazard ratio 1.5; 95% confidence interval, 1.1–1.9), dyspnea at rest (adjusted hazard ratio 1.7; 95% confidence interval, 1.1–2.5), and fasciculation of spinal muscles (adjusted hazard ratio 1.5; 95% confidence interval, 1.2–2.0).

3.5. Mortality risk groups (Table 3)

The two most powerful independent predictors of survival, age at diagnosis and site of onset, enabled us to identify eight subgroups of patients, each with a distinct mortality risk: (1) patients of an age of 40 or younger with a median survival of 5.0 years and a 5- and 10-year
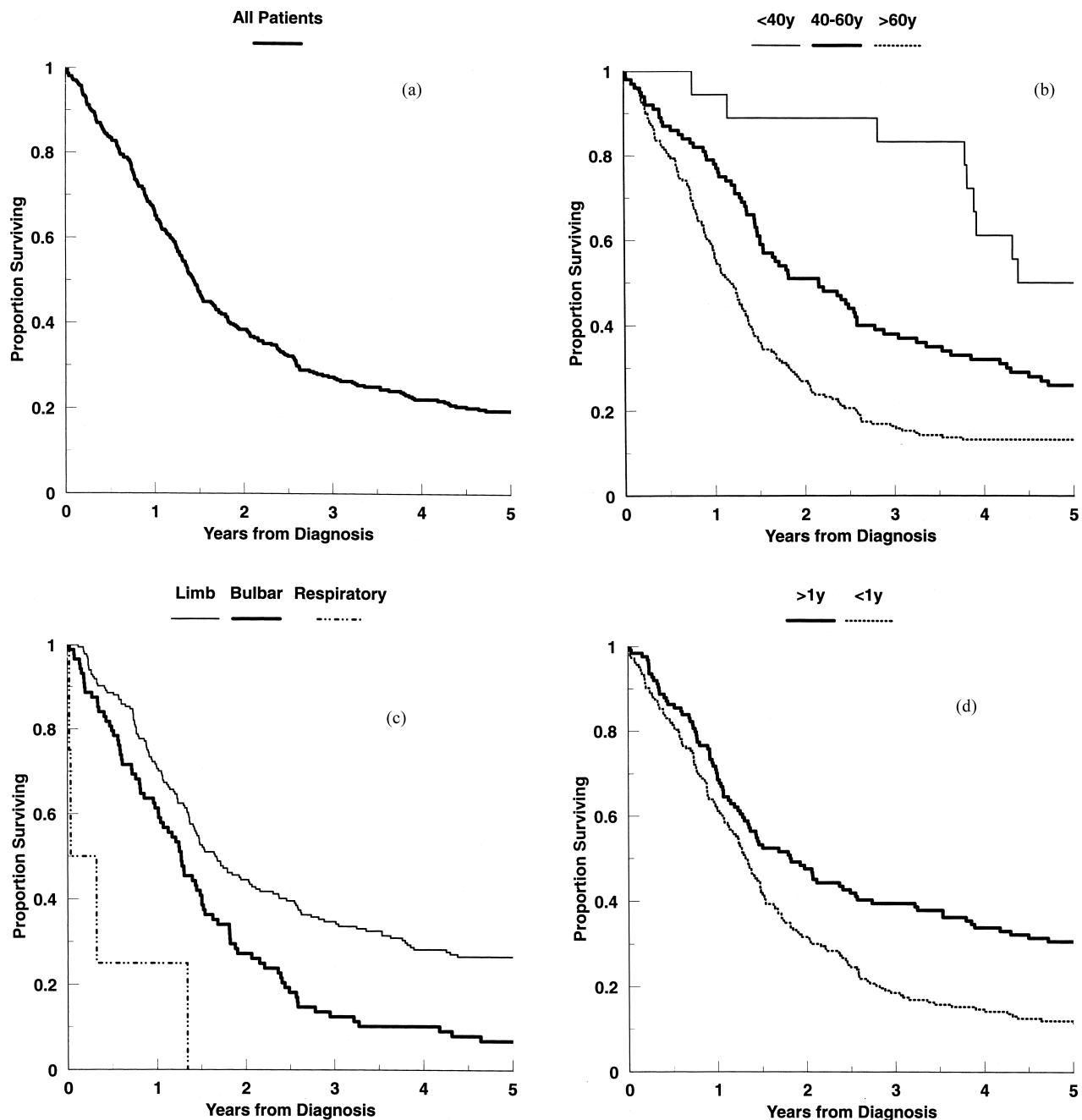
Fig. 2. Survival from diagnosis in 307 patients with amyotrophic lateral sclerosis for the entire study population (panel A), by age at diagnosis (panel B), by site of onset (panel C), and by delay from initial weakness to diagnosis (panel D).

survival of 50 and 44%, respectively; (2) limb-onset males diagnosed at an age between 40 and 60 with a median survival of 3.4 years and a 5- and 10-year survival of 41 and 36%; (3) limb-onset, middle-aged females with a median survival of 1.8 years and a 5- and 10-year survival of 18 and 14%; (4) bulbar-onset, middle-aged patients with a median survival of 1.8 years and a 5- and 10-year survival of 12 and 12%; (5) limb-onset men above the age of 60 with a median survival of 1.4 years and a 5- and 10-year survival of 18 and 7%; (6) limb-onset, older women with a median survival of 1.0 year and a 5- and 10-year survival of 16 and 11%; (7) bulbar-onset, older patients with a median survival of 1.0 year and a 5- and 10-year survival of 5 and 5%; and finally, (8) the highest mortality risk in patients presenting with truncal weakness with a median survival of 2 months and no patients alive 5 years after diagnosis. The percentage of patients in the various subgroups surviving 1, 2, 3, 4, 5, and 10 years after diagnosis in the various mortality risk groups are listed in Table 3.

Table 3
Subgroups of patients with amyotrophic lateral sclerosis, characterized by distinct mortality risk, stratified by age at diagnosis, site of onset, and sex

Subgroup[a]	Percent (95% CI) of patients surviving diagnosis						Median survival		
	1 year	2 years	3 years	4 years	5 years	10 years	Years	(95% CI)	N
≤40 years	94 (84–99)	89 (74–99)	83 (66–99)	61 (39–84)	50 (27–73)	44 (21–67)	5.0	(3.9–[b])	18
40–60 years, limb onset, males	78 (65–91)	61 (46–76)	51 (36–67)	41 (26–57)	41 (26–57)	36 (21–51)	3.4	(1.2–12.9)	41
40–60 years, limb onset, females	86 (72–99)	45 (25–66)	36 (16–56)	27 (9–46)	18 (2–34)	14 (0–28)	1.8	(1.2–4.3)	22
40–60 years, bulbar onset	84 (70–98)	48 (28–68)	20 (4–36)	20 (4–36)	12 (0–25)	12 (0–25)	1.8	(1.4–2.6)	25
>60 years, limb onset, males	69 (58–81)	34 (22–46)	23 (12–33)	19 (10–29)	18 (8–27)	7 (0–14)	1.4	(0.9–2.6)	62
>60 years, limb onset, females	47 (32–61)	26 (13–39)	16 (5–27)	16 (5–27)	16 (5–27)	11 (1–20)	1.0	(0.6–2.1)	43
>60 years, bulbar onset	48 (36–61)	18 (8–27)	8 (1–15)	5 (0–10)	5 (0–10)	5 (0–10)	1.0	(0.5–1.7)	62
Truncal onset	25 (0–67)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.2	(0.1–0.8)	4

Values are percentages (95% CI) of patients surviving after diagnosis, median (95% CI) survival in years or number of patients; CI, confidence interval; N, number of patients.
[a]Either age, site of onset, or sex, unless specified.
[b]Survival after follow-up period of more than 17 years.

4. Discussion

We found that the mortality risk of patients with ALS did not remain constant through the disease. Mortality was at its maximum in the second year after diagnosis and declined considerably thereafter. Patients who survived diagnosis 6 years or more, had almost the same life expectancy as their healthy coevals. In addition, we observed associations between mortality and age at diagnosis, site of onset, and the delay from initial weakness to diagnosis. The better prognosis of patients presenting with limb weakness was not observed in females.

The characteristics and survival of our study population were similar to those, found in other West-European and North-American series (Mulder and Howard, 1976; Juergens et al., 1980; Uebayashi et al., 1983; Kondo and Hemmi, 1984; Mortara et al., 1984; Gubbay et al., 1985; Chazot et al., 1986; Caroscio et al., 1987; Scarpa et al., 1988; Jablecki et al., 1989; Christensen et al., 1990; Chancellor et al., 1993; Eisen et al., 1993; Norris et al., 1993; Haverkamp et al., 1995). By applying strict diagnostic criteria, we have excluded patients with diseases distinct from ALS, especially with progressive spinal muscular atrophy who are known to have a better prognosis (Norris et al., 1993) and possibly explain the longer survivorship in studies with less strict inclusion criteria (Gubbay et al., 1985; Caroscio et al., 1987). Furthermore, we preferred to study prognostic factors from the date of diagnosis, because in many patients, the onset of weakness is poorly defined and patients have a considerable recall bias for it. Also, the date of diagnosis is the first opportunity for a neurologist to estimate prognosis, to make decisions about patient management, and to include patients in clinical trials. However, we may have missed patients with rapidly progressive disease who died before diagnosis.

Predictions from a hospital-based study like ours may have limited validity for population-based patient registers. Rapidly deteriorating patients may not survive until refer-

ral to an academic centre or may be too ill to go there, whereas younger patients are more likely to seek a second opinion. Also, antibiotics, tube-feeding, and symptomatic treatment, are more commonly given in specialized centres. Therefore, patients with ALS seen in academic hospitals may have a relatively better prognosis. On the other hand, patients with a very mild disease progression may not bother to get medical care elsewhere.

The significantly reduced survival of older patients in our study is in accordance with previous studies (Juergens et al., 1980; Uebayashi et al., 1983; Kondo and Hemmi, 1984; Caroscio et al., 1987; Jablecki et al., 1989; Christensen et al., 1990; Chancellor et al., 1993; Eisen et al., 1993; Norris et al., 1993; Haverkamp et al., 1995) and proved not to result from a rise in expected mortality only. The mechanism, by which disease progression in ALS speeds up with increasing age, is unknown. However, the loss of motor neurons with aging may explain why the disease has a more rapid course if the onset falls later in life (McComas et al., 1973). A second explanation is that the elderly may receive less intensive symptomatic care.

After correcting for age as confounding factor, we found a better prognosis in patients with disease of limb onset, but in males only. The distinct predictive value of site of onset between males and females has not been reported before and is yet unexplained. Bulbar patients may die earlier due to an earlier involvement of respiratory muscles, a higher rate of respiratory complications, malnutrition, and dehydration, but this applies to both sexes. The association between site of onset and survival is still debated in literature. Whereas most investigators found an increased mortality in patients presenting with bulbar signs and symptoms (Mulder and Howard, 1976; Uebayashi et al., 1983; Kondo and Hemmi, 1984; Mortara et al., 1984; Caroscio et al., 1987; Christensen et al., 1990; Chancellor et al., 1993; Norris et al., 1993), some failed to confirm this or found no prognostic value after correcting for age (Juergens et al., 1980; Jablecki et al., 1989; Eisen et al., 1993; Haverkamp et al., 1995). The lack of unanimity may

be caused by differences in symptomatic care or an imbalance in other risk factors. Moreover, in agreement with Norris et al. (1993), we found that patients with initial weakness of respiratory muscles without limb or bulbar symptoms, had the worst prognosis with a survival of only a few months. Conversely, patients with an unusual long disease duration were all young males below the age of 40, who presented with limb weakness. Although the number of patients is small, prognostically they should be considered as distinct subgroups.

In the present series, patients with a long delay between initial weakness and diagnosis had a prolonged survival. Because the diagnostic delay was mainly related to patient delay, this may suggest that those with a slower disease progression are later referred or adapt to first weakness for a longer time before they visit a neurologist. These findings agree with those of Haverkamp et al. (1995), who identified the delay between onset of symptoms and first neurological examination as a significant predictor of survival.

Based on survival predictors, we have identified subgroups of ALS patients with distinct mortality risk. Especially, prognosis of males with limb onset, younger patients, and of patients with initial truncal weakness differed from that of all other categories of ALS patients. These findings have several consequences for the planning of symptomatic care. Symptomatic care and necessary appliances in older, bulbar-onset patients should be requested immediately, and provided within an extremely short time. Conversely, in younger patients and males with limb-onset, more time is available for stepwise symptomatic treatment.

The results of our study emphasize the difficulties to be anticipated in designing and evaluating therapeutic trials in ALS. In future trials, the randomization scheme should be adjusted for important survival predictors: age, site of onset, delay from initial weakness to diagnosis, and disease duration since diagnosis. Because differences in prognostic factors between treatment groups at baseline interfere with trial outcome, they should be incorporated in the analysis of trial results. Furthermore, it may be argued that treatment effects gain credibility if obtained during the period of high mortality and that patients with a disease duration of 6 or more years should not enter clinical trials, because they have almost no disease-specific excess mortality. Finally, potential treatment of ALS will be difficult to evaluate early in the disease: usually, the disease is far advanced at diagnosis. The median delay between onset and diagnosis in our study was 10 months or about one-third of the total disease duration, similarly to the results reported by others (Juergens et al., 1980; Mortara et al., 1984; Chazot et al., 1986; Christensen et al., 1990; Tysnes et al., 1991; Norris et al., 1993; Haverkamp et al., 1995).

We conclude that the annual mortality risk in ALS does not remain constant throughout the disease that major prognostic factors are age, site of onset, and the diagnostic

delay. However, our findings do not allow for reliable predictions of survival time in individual patients. Although prognostic factors were identified, there is still an unexplained variability within risk groups, indicating other yet unknown prognostic factors. A search for these factors remains an important task in ALS research.

Acknowledgements

References

Beck, J.R., 1988. Markov models of natural history. J. Clin. Epidemiol. 41, 619–621.

Brooks, B.R., 1994. World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. J. Neurol. Sci. 124 (Suppl), 96–107.

Caroscio, J.T., Mulvihill, M.N., Sterling, R., Abrams, B., 1987. Amyotrophic lateral sclerosis. Its natural history. Neurol. Clin. 5 (1), 1–8.

Chancellor, A.M., Slattery, J.M., Fraser, H., Swingler, R.J., Holloway, S.M., Warlow, C.P., 1993. The prognosis of adult onset motor neuron disease: a prospective study based on the Scottish motor neuron disease register. J. Neurol. 240, 339–346.

Chazot, F., Vallat, J.M., Hugon, J., Lubeau, M., Dumas, M., 1986. ALS in Limousin (Limoges area, France). Neuroepidemiology 5, 39–46.

Christensen, P.B., Hojer-Pedersen, E., Jensen, N.B., 1990. Survival of patients with amyotrophic lateral sclerosis. Neurology 40, 600–604.

Cox, D.R., 1972. Regression models and life tables. J. R. Stat. Soc. B. 34, 187–220.

Eisen, A., Schulzer, M., MacNeil, M., Pant, B., Mak, E., 1993. Duration of amyotrophic lateral sclerosis is age dependent. Muscle Nerve 116, 27–32.

Gubbay, S.S., Kahana, E., Zilber, N., Cooper, G., Pintov, S., Leibowitz, Y., 1985. Amyotrophic lateral sclerosis. A study of its presentation and prognosis. J. Neurol. 232, 295–300.

Haverkamp, L.J., Appel, V., Appel, S.H., 1995. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. Brain 118, 707–719.

Jablecki, C., Berry, C., Leach, J., 1989. Survival prediction in amyotrophic lateral sclerosis. Muscle Nerve 12, 833–841.

Juergens, S.M., Kurland, L.T., Okazaki, H., Mulder, D.W., 1980. ALS in Rochester, Minnesota, 1925–1977. Neurology 30, 463–470.

Kaplan, E.L., Meier, P., 1958. Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. 53, 457–481.

Kondo, K., Hemmi, I., 1984. Clinical statistics in 515 fatal cases of motor neuron disease. Neuroepidemiology 3, 129–148.

Leigh, P.N., Ray-Chaudhuri, K., 1994. Motor neuron disease. J. Neurol. Neurosurg. Psychiatry 57, 886–896.

Louwerse, E.S., Sillevis Smitt, P.A.E., de Jong, J.M.B.V., 1991. Differential diagnosis of sporadic amyotrophic lateral sclerosis (ALS), progressive spinal muscular atrophy (SMA) and progressive bulbar palsy (PBP) in adults. In: De Jong, J.M.B.V. (Ed.), Diseases of the Motor System. Handbook of Clinical Neurology, vol. 15 (59). Elsevier, Amsterdam, pp. 383–423.

McComas, A.J., Upton, A.R.M., Sica, R.E.P., 1973. Motoneurone disease and ageing. Lancet i, 1477–1480.

Mortara, P., Chio, A., Rosso, M.G., Leone, M., Schiffer, D., 1984. Motor

neuron disease in the province of Turin, Italy, 1966–1980: survival analysis. J. Neurol. Sci. 66, 165–173.

Mulder, D.W., Howard, F.M., 1976. Patient resistance and prognosis in amyotrophic lateral sclerosis. Mayo Clin. Proc. 51, 537–541.

Munsat, T.L., Andres, P.L., Finison, L., Conlon, T., Thibodeau, L., 1988. The natural history of motoneuron loss in amyotrophic lateral sclerosis. Neurology 38, 409–411.

Norris, F., Shepherd, R., Denys, E., Kwei, U., Mukai, E., Elias, L., Holden, D., Norris, H., 1993. Onset, natural history and outcome in idiopathic motor neuron disease. J. Neurol. Sci. 118, 48–55.

SAS Institute, Cary, North Carolina, 1988. SAS/STAT and SAS/GRAPH User's Guide, SAS Language Guide, SAS Procedure GUIDE. Release 6.03.

Scarpa, M., Colombo, A., Panzetti, P., Sorgato, P., 1988. Epidemiology of amyot rophic lateral sclerosis in the province of Modena, Italy. Influence of environmental exposure to lead. Acta Neurol. Scand. 77, 456–460.

Tysnes, O.B., Vollset, S.E., Aarli, J.A., 1991. Epidemiology of amyotrophic lateral sclerosis in Hordaland county, western Norway. Acta Neurol. Scand. 83, 280–285.

Uebayashi, Y., Yase, Y., Tanaka, H., Shimada, Y., Toyokura, Y., 1983. Prognosis of motor neurone disease in Japan. Neuroepidemiology 2, 243–256.

Verheul, H.A., Dekker, E., Bossuyt, P.M.M., Moulijn, A.C., Dunning, A.J., 1993. Background mortality in clinical survival studies. Lancet 341, 872–875.