Familial Amyotrophic Lateral Sclerosis, 1850-1989: A Statistical Analysis of the World Literature

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ABSTRACT: We present clinical and pathologic data on four previously unreported familial ALS pedigrees and review and analyze by descriptive and exploratory statistical techniques all published cases of familial ALS (1850-1989). In contrast to the age-dependent incidence of sporadic ALS, the age of onset of familial ALS is normally distributed about a mean of 45.7 years (std. dev. 11.3 years). Survival curves for the familial ALS data also demonstrate a skewed distribution with a median survival time of 24 months with 74% surviving at 12 months, 48% at 24 months and 23% surviving at 60 months. The patient characteristics of age at onset of disease, sex and focus of disease onset are unrelated variables and age at onset of disease is the only predictor of survival (Cox's proportional hazard model, chi-square 14.74, p = 0.0001). By applying accelerated failure time models with a log-normal baseline distribution, estimated probabilities for survival adjusted by age at onset were calculated. It was found that the older the age at disease onset, the shorter the survival.

RÉSUMÉ: La sclérose latérale amyotrophique familiale, 1850-1989: une analyse statistique de la littérature mondiale. Nous présentons des données cliniques et histopathologiques sur quatre pedigrees de SLA familiale qui n'ont encore jamais été rapportés et nous revoyons et analysons par des techniques statistiques descriptives et exploratrices tous les cas de SLA familiale publiés (1850 - 1989). Contrairement aux cas sporadiques de SLA où l'incidence est dépendante de l'âge, l'âge de début dans la SLA familiale est distribué normalement autour de la moyenne qui est de 45.7 ans (écart type 11.3 ans). Les courbes de survie pour la SLA familiale montrent également une distribution dyssymétrique avec un temps de survie médian de 24 mois, 74% des patients étant vivants à 12 mois, 48% à 24 mois et 23% à 60 mois. Les caractéristiques du patient en ce qui concerne l'âge de début de la maladie, le sexe et le site de début de la maladie sont des variables indépendantes et l'âge au début de la maladie est le seul élément prédictif de la survie (modèle d'analyse de survie de Cox, chi-carré 14.74, p = 0.0001). En appliquant des modèles de temps de survie ayant une distribution de base log-normale, nous avons estimé la probabilité de survie ajustée pour l'âge de début. Nous avons trouvé que plus l'âge de début était tardif, plus la survie était courte.

In the century since the seminal descriptions of amyotrophic lateral sclerosis (ALS) by Aran,[1,2] Duchenne[3,4] and Charcot,[5] ALS has remained an etiological enigma. This is due in part to a clinical presentation, as a rule, of only upper and lower motor neuron involvement despite a varied morphological picture in the different forms of the disease, viz. classical sporadic, familial and Western Pacific ALS. Corresponding to the clinical presentation, the most consistent pathological findings in all forms of ALS are corticospinal and lower motor neuron degeneration. However, in the familial type, there are no clinical correlates to the frequent additional findings of degeneration of the posterior columns, dorsal spinocerebellar tracts and nucleus dorsalis of

Clarke.[6,7] Also in Western Pacific ALS the characteristic deposition of neurofibrillary proteins in subcortical regions is usually symptomatically silent.[8,9] Thus, ALS is a clinically distinctive disorder of the motor system but there are at least three pathological variants with the same clinical features.

The classical sporadic form of ALS is the most common form of the disease — the hallmark of which is a relentlessly progressive and widespread wasting of skeletal muscle accompanying upper and lower motor neuron degeneration.[10-12]. The Western Pacific form of ALS, once endemic to Guam, Western New Guinea and the Kii Peninsula, while clinically similar to the sporadic disease, shows a marked tendency towards familial

clustering. Although initially interpreted as an inherited variant of classical sporadic ALS, it is now clear that an environmental insult has played a pivotal role in the genesis of this focus.[13-16] However, until the early epidemiological investigations of the Guamanian focus of ALS, the possibility of classical ALS having a genetic component was considered remote.

Our current understanding of the inheritance characteristics of familial ALS is based largely on studies conducted within the last 30 years[7,17-23] which have demonstrated that familial ALS is predominantly inherited as an autosomal dominant trait. Although this is also suggested by a limited number of twin studies,[24-26] at least one set of monozygotic twins was discordant for the disease.[27] Thus it still remains to be determined if the inherited variant of ALS is causally related to a specific environmental insult in a susceptible population (producing a familial clustering) or due to the transmission from one generation to the next of a specific gene defect.

In order to further delineate the clinical characteristics of familial ALS, we have statistically analyzed the data from all published cases of this variant of ALS (1850-1989) and explored the relationships between survivability and the clinical characteristics of the patients. In conjunction with this, we present data on four previously unreported pedigrees of familial ALS.

FAMILY HISTORIES

Family CS: Four generations of this family developed ALS. Patient I-1, a male born in 1869, died in 1912 from a "muscle disorder" of short duration. Patient II-2, the daughter of I-1, died at age 50 years following a 12 month illness marked by dysphagia, dysarthria and right arm weakness. Both siblings died of unrelated causes. The only offspring of II-2 died at age 45 years following a 12 month illness characterized initially by dysarthria and dysphagia. This progressed to include palatal paresis, symmetric tongue wasting with fasciculations, absent gag reflex and a brisk jaw jerk. The deep tendon reflexes were normal although the sign of Babinski was present on the left. An electromyogram (EMG) was compatible with a lower motor neuron disorder. An autopsy performed elsewhere confirmed the diagnosis of ALS.

The proband, IV-2, developed right thigh twitching and right leg weakness at age 44 years. During the 9 month course of her illness, the patient developed tongue and diffuse four limb atrophy with fasciculations, symmetric global lower extremity weakness and bilateral signs of Babinski. An EMG showed diffuse four limb denervation with normal conduction velocities. Two brothers, aged 48 and 38 years, are healthy. A son, age 21 years, and three daughters (aged 19, 17 and 13 years) are also well.

At autopsy, the anterior spinal nerve roots demonstrated a distinct thinning and greyish discoloration. Histologically, the premotor cortex showed chromatolytic pyramidal neurons with hyaline inclusions. Neurofibrillary tangles were occasionally found throughout the motor and premotor cortex and in the postcentral gyrus. The hippocampus was normal. Chromatolysis and inclusions were seen in the Vth (motor), VIth, VIIth and XIIth nuclei, and nucleus ambiguus. Mild pallor of the corticospinal tracts was present. At all levels of the spinal cord, a marked loss of anterior horn cells with gliosis was present, as were ghost cells, hyaline inclusions, increased lipofuscin pigmentation, eosinophilic globular inclusions and corpora amylacea in the adjacent white matter. Additionally, in the lumbar and sacral regions, neuroaxonal swellings, spheroids, neuronophagia and a more striking gliosis were noted. Throughout the spinal cord a mild pallor of the dorsal spinocerebellar tract was noted, accompanied by a loss of cells in the nucleus dorsalis of Clarke. Sections of the tibialis anterior and deltoid muscles demonstrated small fibre grouping and rare regenerating fibres.

Family GE: Two generations of this family are affected. Patient I-1 died at age 49 years after a disease of 4 to 5 years duration marked by diffuse muscle weakness and twitching. The diagnosis at the time of death was ALS.

The proband, II-1, developed right upper extremity weakness at the age of 46 years and died 37 months later with respiratory failure. During the course of the illness, the patient was found to have progressive muscle wasting of all extremities with fasciculations, pathologically brisk deep tendon reflexes with bilateral Babinski signs, and tongue wasting with fasciculations. The sensory exam remained normal. A muscle biopsy showed neurogenic atrophy. An autopsy was not performed. Two male offspring remain healthy.

Patient II-2 developed diffuse fasciculations at the age of 56 years and died 13 months later with diffuse weakness and fasciculations, hyperreflexia with bilateral Babinski signs and, terminally, dysphagia. An EMG demonstrated diffuse denervation. No autopsy was performed.

Family JT: Three generations of this family have ALS. Patient I-1, a female, died at the age of 36 years with "creeping paralysis" — the pseudonym applied to this disease by this family. The only known offspring died at the age of 44 years after a 4 year history of "creeping paralysis". Two of his three offspring have ALS.

Patient III-1 developed facial weakness at the age of 62 years and was found to have an atrophic, slow moving tongue, diffuse weakness and upper extremity fasciculation. Preceding her death 4 months later, bilateral Babinski signs were present. An EMG showed widespread denervation with normal conduction velocities. No autopsy was performed.

Patient III-2 developed right hand wasting and "twitching" of the upper extremities at the age of 64 years and died 20 months later. At the only recorded neurological examination, she was found to have a distal upper extremity weakness with asymmetric interossei wasting, diffuse fasciculations and normal reflexes. An autopsy demonstrated a marked loss of neurons of the hypoglossal nucleus with gliosis and ghost neurons, pallor of the lateral corticospinal tracts, and a diffuse loss of anterior horn cells. The remaining anterior horn cells showed globular eosinophilic inclusions, chromatolysis and ghost cells.

The remaining sibling, III-3, developed diffuse muscle weakness and wasting at the age of 59 years. On examination she was found in
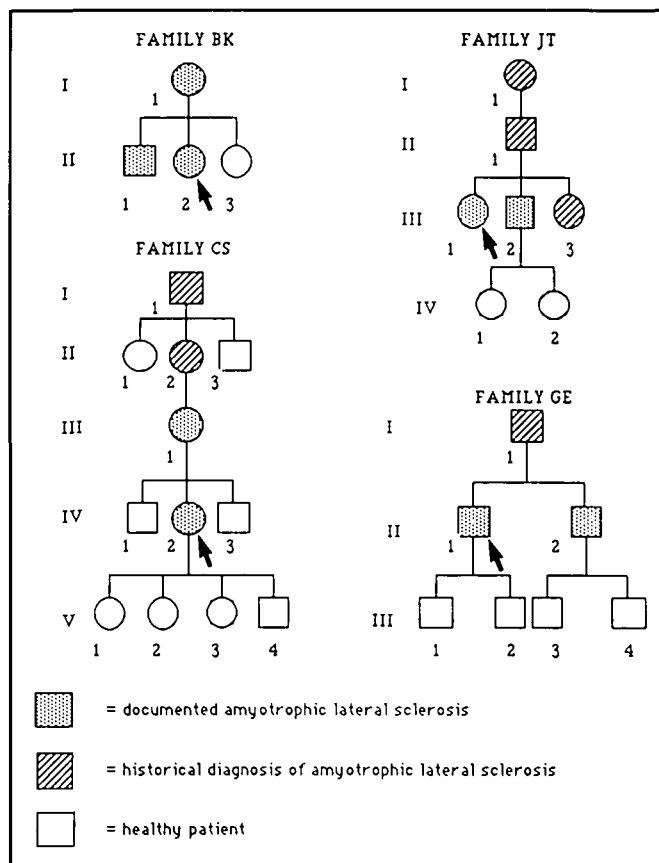

Figure 1 — Family Trees. The proband is indicated by an arrow.

addition to have spasticity and bilateral Babinski responses. No bulbar features were noted.

Family BK: An extensive review of this family's pedigree, extending to European ancestry, failed to reveal any individuals afflicted with a neuromuscular disease apart from the following. The mother, I-1, died at age 48 years following an 18 year history of cramps, wasting and muscle twitching. While carried for many years in a provincial muscular dystrophy registry, her ultimate diagnosis was ALS, confirmed at autopsy.

The proband, II-2, first noted a sensation of "worms" in the right calf, associated with frequent cramps and progressive right leg weakness. One year later she was found to have asymmetric plantar flexion weakness, calf wasting with fasciculations, marked wasting of interossei and intrinsic muscles of the feet, pathologically brisk deep tendon reflexes and bilateral Babinski signs. An EMG one year later showed active denervation in both lower extremities. Ten and a half years after the disease onset, the patient remains alive and has developed bulbar dysfunction.

A sibling, II-1, initially noted lower extremity twitchings and cramps followed six years later by widespread fasciculations, asymmetric upper extremity and interossei wasting, pathologically brisk deep tendon reflexes and a unilateral Babinski sign. No further progression has been noted.

LITERATURE EVALUATION

Case Ascertainment

All reports of familial ALS or familial motor neuron disease (MND) in the world literature were collected and subjected to two levels of scrutiny before inclusion in a final analysis. This yielded 100 families with 309 individual cases in the period from 1850 to 1989. A certain number of reports could be immediately excluded from further analysis in that (i) the cases described did not satisfy the criteria of ALS (7 families), (ii) insufficient history or clinical data was supplied to substantiate a familial categorization (11 families), or (iii) the inherited disease included amyotrophy as a component of another neurodegenerative disorder, hereditary or otherwise (2 families). The remaining 84 families (249 cases), including those of the current authors, underwent a more critical evaluation.

Categorical scores were given to historical, physical, electrophysiological and pathological findings. These values represented a classification index for purposes of statistical analysis and did not imply a specific rank ordering. Historical findings were acceptable if derived from a reliable source (physician or first degree relative giving a complete account) and the clinical findings were derived from an actual recorded assessment. The categorical scores for both history and clinical data are given in Table 1. Electrophysiological assessments (electromyography and nerve conduction studies) were assessed as either (i) not done or done but not compatible with a neurogenic lesion (a score of 0), or (ii) done and compatible with the diagnosis of ALS (a score of 1). Compatibility required evidence for denervation in multiple unrelated spinal segments with normal motor nerve conduction velocities (>75% of normal). In a similar fashion the pathology data were assessed a score of 0 or 1, the latter being those cases with the findings compatible with a histological diagnosis of ALS.

The age of onset was recorded in years (defined as the age at which the patient first noted symptoms) and survival recorded in months (defined as the time of first symptoms to the time of death). Due to the insidious nature of the disease process of ALS, defining the onset of disease is difficult at the best of times. Many case reports did not specify the time of first visit to

a physician, or the first appearance of neurological deficits. However, the first appearance of symptoms (e.g. hand weakness, dysphagia, etc.) was uniformly reported. Similarly, while duration is traditionally taken to be the time from clinical disease onset to the time of treatment onset or physician review, and survival taken as the interval thereafter to either death or completion of the treatment protocol, we have utilized time from first clinical symptom to the death as survival. Where possible, the subjective focus of disease onset (the first site of symptoms as reported by the patient) was recorded as either bulbar, lower motor neuron (LMN), or global. The global category was utilized for those cases in which the subjective onset, as recorded, could not be clearly differentiated into the bulbar or LMN categories. Attempts to further differentiate the focus of onset into proximal or distal did not yield additional information.

For inclusion in the analysis, a case required **at least one** of the following three **categorical** scores: either (i) a history or clinical exam score of 70; (ii) a clinical score of 30 accompanied by an EMG score of 1 (no clinical evidence of LMN disease, but electrophysiological evidence of such); (iii) a pathology score of 1. All history or clinical scores other than these constituted an exclusion from further analysis. In Table 2 the literature evaluation with scores of acceptable reports are listed.

The pedigree was excluded when application of the inclusion criteria left only one acceptable case and required at minimum one affected first degree relative or affected relatives in two generations. In this way it was intended that a true sporadic ALS case occurring in the setting of other diseases (independently or in combination) involving the motor neuron would be excluded.

Table 1: Categorical scores were applied to the cases of familial amyotrophic lateral sclerosis derived from a literature review (1850-1989). Scores were assigned to the variables of history, clinical observations, electromyography and pathology.

History and Clinical Observations:

Observation**	Categorical Score*
Bulbar	10
UMN only	20
Bulbar plus UMN	30
LMN only	40
Bulbar plus LMN	50
UMN plus LMN	60
ALS	70

EMG (electromyography):
  not done = 0
  done and compatible with ALS = 1

Pathology:
  not done = 0
  done and compatible with ALS = 1

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*Categorical Score: this score does not represent a rank ordering of symptoms and signs, rather it is a classification index for purposes of statistical manipulation.

**UMN = upper motor neuron; LMN = lower motor neuron

STATISTICAL METHODS

After application of the inclusion criteria, 53 families (149 cases) remained, 144 of which reported survival times. The data were then subjected to a variety of exploratory and confirmatory analytical methods. In addition to survival times, fairly complete data were available on the patient characteristics (concomitant variables) of age at onset of disease, sex, and focus of disease at onset. In general, we felt that multiple methods of analysis tending to the same conclusions would increase confidence in the conclusions.

In the analyses presented here, we began with simple descriptive measures of the concomitant variables age at onset, sex, and focus of disease and thereafter, using log-linear analysis, determined whether any relationships existed among the independent variables. In determining whether certain patient characteristics might serve as prognostic indicators of survival, we then described the survival curve for familial ALS and explored the general question of whether the various subgroups of concomitant variables (e.g. sex) arose from identical survivor functions. Standard nonparametric comparative techniques were used. To determine those patient characteristics that might be related to survival, we fit Cox's (1972) proportional hazards model.[60] Finally, we compared the results of fitting the proportional hazards model and fully parametric models and developed a simple method for predicting the probability of survival given the patient's age at disease onset.

Standard Descriptive Analysis of Covariables

A histogram of the age at onset data is shown in Figure 2. The ages were normally distributed about a mean of 45.7 years with a standard deviation of 11.3 years (range 20-72 years). A test of fit (normal probability plot) showed that the data followed a normal distribution (p > 0.15). In a normal probability plot, variables that are normally distributed will fall along a straight line — deviations from this indicate a distribution other than normal.

A histogram of survival is displayed in Figure 3. In contrast to the normal distributional curve for the age of onset, the distri-

bution of survival is decidedly skewed. This visual impression was confirmed by the failure of fit of the data to a normal probability plot.

The male:female ratio was 1.36:1. The hypothesis of equal proportions of males and females was tested using the large sample tests statistics, which yielded a value of 1.22 (p = 0.2225) — nonsignificant. Since test statistics did not indicate any difference in the proportions of males to females, the sex ratio does not differ statistically from 1:1.

Prior to investigating possible relationships between the patient characteristics and survival, we performed a series of hierarchical log-linear analyses to examine possible relationships among variables. Information on the focus of disease (global, LMN, bulbar) was available for 126 (87.5%) of the patients in this study. Table 3 shows the cross classification of the 126 patients on these variables. Although age at onset will be treated as a continuous covariate in subsequent analysis, it was dichotomized at 50 years in the present analysis in order to assure a minimum of five observations in each cell and to provide an analysis which would be comparable to traditional studies of sporadic ALS in which age of onset is conventionally dichotomized at 50 years.[61-63] In the log-linear analyses, the model of complete independence between sex, age and focus is an adequate model for describing the data (χ^2 = 10.19; df = 7, p = 0.1780). Subsequent analyses, which described various relationships between the covariables, were also nonsignificant (details available upon request). Thus, no relationship was shown to exist between sex, age, and focus for this population of ALS patients.

Nonparametric Analysis of Covariates: Relationship to Survival

Having demonstrated no relationship between these variables, we next addressed the question of the possible impact that age, sex, and focus might have on survival. Summary data and statistics for 144 ALS patients are presented in Table 4. For each variable, the number of patients in each subgroup, the percent of observations that were censored, the median survival (50th percentile) in months and the proportions surviving (along with their standard errors) after 12, 24, and 60 months, respectively,

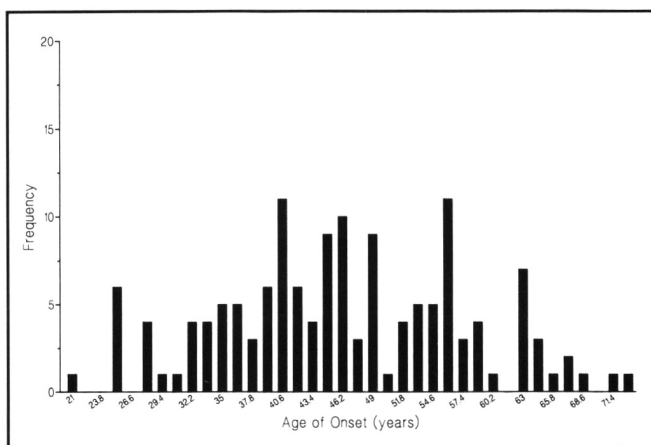*Figure 2 — The age of onset for all cases of familial ALS, illustrated here in a histogram, follows a normal distribution with a mean age of onset of 45.7 years (std. dev. 11.3 yrs).*
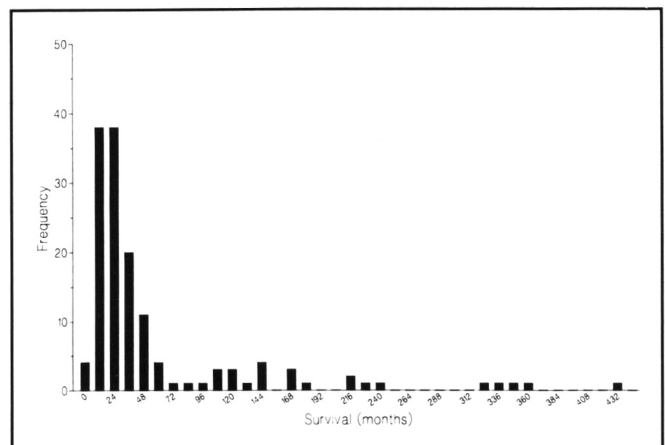

Figure 3 — In contrast to the distribution of age of onset, the survival data for all reported cases of familial ALS is skewed. The histogram also suggests bimodal peaks at approximately 24 months and 144 months.

Table 2: Familial amyotrophic lateral sclerosis — case reports, 1850-1988

Author	Case	Sex	Age of Onset (yrs)	History	Clinical Exam	EMG	Path	Survival (months)	Initial Focus	Comments
Aran, 1850[1,2]	1	M	43	0	70	0	0	24	global	
	2	F	40	70	0	0	0	24	n/a	
	3	F	40	70	0	0	0	24	n/a	
Bernhardt, 1889[28]	III-4	M	40	50	70	0	0	20	distal, UE	
	IV-5	M	32	50	70	0	0	20	proximal, UE	
	IV-3	M	36	50	70	0	0	20	proximal, UE	
Hamilton, 1918[29]	II-1	F	55	70	0	0	0	5	n/a	
	IV-12	M	44	70	70	0	1	11	distal, UE	
Schroeder, 1946[30]	I-1	F	48	70	70	0	0	42	distal, UE	
	I-2	F	52	70	70	0	0	42	bulbar	
	III-1	F	56	0	70	0	0	36	distal, UE	
	III-2	F	63	40	70	0	0	108	global	
de la Vigne & Ahmad, 1952[31]	1	M	45	50	70	0	0	24	bulbar	
	2	M	68	70	0	0	0	24	bulbar	
Kurland & Mulder, 1955[21]	III-23	M	43	0	70	0	0	13	global	
	I-1	M	56	70	0	0	0	24	n/a	
"C Family"	II-2	F	27	70	0	0	0	24	n/a	
(see also Nakano	IV-1	M	39	0	70	0	1	7	n/a	
et al, 1984)[32]	IV-2	M	46	0	70	0	1	8	n/a	
"F Family"	II-8	M	33	50	70	0	0	28	distal, UE	
	III-18	F	25	70	50	0	1	18	global	
	III-21	F	38	0	70	0	0	12	global	
"S Family"	III-5	M	55	0	70	1	1	17	distal, LE	
	III-6	M	33	0	70	0	0	12	global	
"B Family"	II-6	M	50	40	70	1	0	9	global	
	II-4	F	58	50	70	0	0	8	global	
	II-3	M	25	40	70	0	0	9	global	
Boudin & Barbizet, 1956[33]	III-1	M	42	70	70	1	0	9	distal, LE	
	II-3	M	47	70	0	0	0	9	n/a	
Perry & Nesky, 1958[34]	1	M	37	50	70	0	0	36	distal, UE	
	2	F	49	50	70	0	0	36	global	
Alajouanine & Nick, 1959[35]	2	M	66.5	70	70	0	0	18	global	
	3	M	58	70	70	0	0	4	bulbar	
Campanella & Bigi, 1959[36]	III-8	M	25	70	0	0	0	360	global	
	III-11	M	40	70	0	0	0	336	global	
	III-14	M	40	70	70	0	0	240	distal, UE	
Dierssen Gervas, 1959[37]	II-4	M	54	70	70	0	0	24	bulbar	still alive
	I-2	M	58	70	0	0	0	120	bulbar	
	0-2	M	n/a	70	0	0	0	120	bulbar	
Faveret, 1959[18]	III-11	M	39	50	70	0	0	18	bulbar	still alive
"COD. Famille"	III-1	M	31	70	10	0	0	90	global	
"NER. Famille"	II-13	F	56	70	70	0	0	12	bulbar	
	II-4	F	40	70	0	0	0	12	global	
Engel et al, 1959[17]	V-56	M	36	70	70	0	1	12	distal, UE	
"A Family"	III-9	F	51.5	70	0	0	0	18	distal, LE	
	III-8	M	35	70	0	0	0	24	n/a	
"B Family"	IV-4	F	46	70	70	1	1	20	global	
(see also Hirano et al, 1967)[38]	IV-2	M	54	50	50	1	1	9	global	
Aydillo, 1960[39]	II-8	M	20	70	70	0	0	180	n/a	still alive
	II-5	M	28	70	70	0	0	228	bulbar	
	I-2	M	38	70	0	0	0	144	n/a	

TABLE 2: Familial amyotrophic lateral sclerosis – case reports, 1850-1988 — cont'd.

Author	Case	Sex	Age of Onset (yrs)	History	Clinical Exam	EMG	Path	Survival (months)	Initial Focus	Comments
Wohlfart, 1960[40]	I-1	M	37	70	70	0	0	24	distal, UE	
	1-6	M	40	70	70	1	0	24	distal, UE	
	II-1	M	63	60	60	0	0	30	distal, UE	
	II-2	F	48	70	70	0	0	16	bulbar	
	1	M	65	70	70	1	0	n/a	global	
	2	F	52	70	70	0	0	12	bulbar	
Espinosa et al, 1962[41]	III-2	M	51	0	70	0	1	24	proximal, LE	
	III-4	F	24	70	70	0	0	348	distal, UE	still alive
	III-8	F	34	0	70	1	0	120	distal, UE	
	III-9	F	32	50	70	1	0	120	global	
Liberati & Pompili, 1964[42]	II-1	M	42	70	70	1	0	144	global	
	II-3	F	51	50	70	1	0	108	global	
	III-3	F	34	70	70	1	0	12	global	still alive
Roe, 1964[43]	I-1	F	53	0	70	0	0	12	bulbar	
	II-3	F	48	0	70	0	0	30	proximal, UE	
	II-5	F	44	0	70	0	0	12	global	
Boudouresques et al, 1966[44]	I-1	M	59	70	70	0	0	12	bulbar	
	I-2	M	28	70	70	0	0	37	bulbar	
Fleck & Zurrow, 1967[45]	II-4	F	63	50	50	1	1	8	bulbar	
	II-3	F	56	50	70	1	0	48	n/a	still alive
Avanzini et al, 1968[46]	III-8	M	47	70	70	1	0	48	proximal, UE	
	III-9	M	48	70	70	1	0	24	global	
	III-1	M	40	70	70	0	0	84	proximal	
Dazzi & Finizio, 1969[47]	I-1	F	n/a	70	0	0	0	n/a	n/a	
	II-1	F	46	70	0	0	0	48	bulbar	
	II-3	F	46	70	0	0	0	10	global	
	III-2	M	53	50	70	0	0	19	bulbar	
	III-3	F	46	70	70	1	0	18	bulbar	still alive
	III-5	F	42	0	70	0	0	n/a	global	still alive
	III-9	F	40	70	70	1	0	36	bulbar	
Farmer & Allen, 1969[48]	1	M	35	70	70	0	1	36	bulbar	
	2	M	51	70	70	0	1	9	proximal, UE	
Metcalf & Hirano, 1971[49]	IV-22	M	44	0	70	0	1	168	distal, LE	
	IV-23	M	44	50	70	0	0	36	n/a	
Dinsky et al, 1975[50]	II-2	M	72	70	70	0	1	48	global	
	III-2	F	50	70	70	0	1	60	global	
	III-5	M	42	70	70	1	0	24	bulbar	
Alter & Schaumann, 1976[51] "M Family"	IV-31	M	49	70	70	1	1	11	global	
	IV-26	M	48	40	70	0	1	25	distal, UE	
	IV-25	M	49	70	70	0	1	15	distal, UE	
	III-2	M	37	70	0	0	0	18	global	
"O Family"	IV-34	F	41	70	70	1	1	36	distal, LE	
	IV-35	F	53	70	70	0	0	30	distal, UE	
	III-11	F	56	70	70	0	0	36	distal, UE	
	III-13	M	48	40	60	0	1	48	bulbar	
Gardner & Feldmahn, 1976[52]	1	F	33	70	70	0	1	7	bulbar	
	2	F	63	70	70	0	1	13	global	
	3	F	42	70	50	0	1	18	global	
Horton et al, 1976[7]	III-5	M	57	0	70	1	1	24	distal, UE	
"Family #3"	II-3	F	71	0	70	0	0	12	bulbar	
"Family #2"	III-4	M	54	0	50	0	1	36	distal, LE	
	III-5	F	54	0	70	0	1	36	global	

Table 2: Familial amyotrophic lateral sclerosis — case reports, 1850-1988 — cont'd.

Author	Case	Sex	Age of Onset (yrs)	History	Clinical Exam	EMG	Path	Survival (months)	Initial Focus	Comments
"Family #4"	III-13	F	63	0	70	1	0	24	bulbar	
	III-16	F	56	0	70	0	0	32	distal, UE	
"Family #7"	III-6	F	57	70	70	1	0	36	distal, LE	
	III-2	M	66	70	70	1	1	12	global	still alive
"Family #12"	IV-16	M	36	0	70	1	0	144	distal, LE	still alive
	IV-3	M	44	0	70	0	1	168	distal, LE	
	IV-23	M	33	0	70	0	0	132	global	
	IV-24	F	28	0	70	0	0	324	distal, LE	
"Family #13"	III-2	M	45	0	70	1	0	108	proximal, LE	still alive
	III-5	M	44	0	70	0	0	36	proximal, LE	still alive
Swerts & van den Bergh, 1976[53]	II-5	F	43	60	70	0	0	24	distal, UE	
	II-6	M	36	70	0	0	0	24	n/a	
	II-2	M	29	60	70	0	0	24	global	
	II-8	M	39	70	70	0	0	12	global	
	III-21	M	36	70	70	1	0	12	global	
Estrin, 1977[24]	III-3	M	57	40	70	1	0	16	global	still alive
	III-4	M	55	40	70	1	0	36	distal, UE	still alive
Giménez-Roldán, 1977/1978[54, 55]	II-5	F	55	70	0	0	0	24	global	
	III-4	F	58	70	70	1	0	60	distal, UE	
	III-6	F	40	10	70	0	0	144	bulbar	
Hestnes & Mellgren, 1980[56]	III-1	M	64	40	70	0	0	36	global	still alive
	II-7	F	72	70	70	0	0	36	global	
Husquinet & Franck, 1980[57]	V-13	M	44.5	70	70	0	0	54	proximal, UE	
	V-23	M	45	70	70	1	0	72	distal, UE	
	V-28	F	n/a	70	70	1	0	12	distal, UE	still alive
	VI-25	M	44	70	0	0	0	60	distal, UE	
	V-18	M	45	70	70	1	0	48	global	still alive
Alberca et al, 1981[58]	II-3	F	38	70	70	1	0	216	global	
	III-6	M	25	70	70	1	0	168	global	still alive
	II-5	M	24	40	70	1	0	432	global	still alive
Hawkes et al, 1984[59]	IV-1	M	63	70	70	1	1	6	global	
	IV-18	M	39	50	70	0	1	3	global	
	IV-20	F	47	50	70	1	1	5	global	
Gregoire et al, 1987[11]	III-1	F	55	0	70	0	0	n/a	n/a	
	III-2	F	54	70	0	0	0	48	n/a	
Current Authors	II-2	F	41	70	0	0	0	12	bulbar	
"CS Family"	III-1	F	45	70	70	1	0	10	bulbar	
	IV-2	F	44	70	70	1	1	9	global	
"T Family"	I-1	F	35	70	0	0	0	12	n/a	
	II-1	M	40	70	0	0	0	48	n/a	
	III-1	F	62	70	70	1	0	9	bulbar	
"GE Family"	I-1	M	45	70	0	0	0	60	global	
	II-1	M	56	70	70	1	0	37	global	
	II-2	M	57	70	70	1	0	13	global	
"BK Family"	I-1	F	30	70	60	0	1	216	n/a	
	II-2	F	31	70	70	1	0	n/a	distal, LE	still alive

Abbreviations: UE = upper extremity; LE = lower extremity; n/a = data not available; global = history did not allow for precise differentiation of bulbar vs lower motor neuron onset; path = pathology

were recorded. Statistics were obtained following the Kaplan-Meier (product limit) method.[64,65]

Survivorship Taken Without Respect to Grouping Variable

For all patients taken collectively, the median survival time was 24 months. Table 4 shows that 74% of patients survived more than 12 months following the onset of the disease, 48% survived more than 24 months and 23% survived more than 60 months. Hence, one-, two- and five-year periods correspond approximately to the first, second, and third quartiles (25, 50, and 75th percentiles). Figure 4 shows a Kaplan-Meier survival curve depicting this situation.

Prognostic Variables for Survival

Age — Table 5 reports the results for ALS patients divided into two age groups, those 50 years or younger and those over 50 years. The proportions surviving in the two groups after 12 and 24 months are similar, falling within 2 standard errors of each other. However, at 60 months only 10% of the patients in the over 50 group survived, compared to 28% of the under 50 group. Figure 5 shows the survival curves for each group and suggests a similarity between the two age groups for approximately the first 24 months and an apparently distinct separation by 60 months.

To determine whether this perceived age-dependent difference in survival time was statistically significant, two nonpara-

metric statistical tests were performed — the log rank test[65,(pp 16-19)] and Gehan's generalized Wilcoxon test.[66] The log rank test, which places more weight on longer survival times, is significant at the 0.05 level ($\chi^2 = 5.46$, 1 df, p = 0.0194). However, Gehan's generalized Wilcoxon test, which places greater emphasis on early survival times, is not significant ($\chi^2 = 1.86$, 1 df, p = 0.1721). It appears that the two age groups differ primarily at longer survival times where the risk of death is greater in the over 50 subgroup.

Sex — The median survival time for both sexes was 24 months with no difference in survival rates between the sexes (log rank test: $\chi^2 = 2.18$, 1 df, p = 0.1397; Gehan's generalized Wilcoxon test: $\chi^2 = 1.45$, 1 df, p = 0.2272, both nonsignificant).

Disease Focus — Focus of onset data were available for 126 (87.5%) patients. The median survival time for bulbar and global categories was 24 months, while median survival time for the LMN category was 32 months. At 60 months the proportions surviving for the LMN and global groups are equivalent (0.25 and 0.26 with s.e.'s of 0.07) and the corresponding proportion for the bulbar group (0.12, s.e. of 0.07) appears slightly lower but remains within 2 standard errors of the others. The log rank test ($\chi^2 = 2.87$, 2 df, p = 0.2381), and the generalized Wilcoxon test ($\chi^2 = 4.74$, 2 df, p = 0.0934) were both nonsignificant at the 0.05 level, demonstrating no significant differences in survivorship related to focus of disease onset.

Proportional Hazards and Accelerated Failure Time Models

In the preceding analysis, we examined how the concomitant variables age, sex and disease focus might be related to survival and found that age appears to be the most promising candidate as a prognostic variable. In this section, we apply Cox's proportional hazards model[60] and accelerated failure time models[65] to determine whether concomitant variables acting conjointly help to explain survival time in familial ALS patients (details presented in Appendix I).

Table 5 shows results for three separate fittings of the proportional hazards model to ALS data. In this analysis, age is considered as a continuous covariate ranging from 24 to 72 years (for

Table 3: Observations Cross-classified by Sex, Age at Onset (Dichotomized), and Focus of Onset of Disease.

Sex	Age	Focus of Onset		
		Bulbar	LMN*	Global
Male	≤ 50	6	24	21
	> 50	6	7	10
Female	≤ 50	8	8	14
	> 50	8	7	7

*LMN – lower motor neuron

TABLE 4: Summary Data for Three Variables Related to Survival (First Symptom to Death) Among 144 Familial ALS Patients.

Variable & Levels	# Patients (% Censored)	Median Survival (Months)	Proportion Surviving After**		
			12 mo	24 mo	60 mo
All	144 (11.81)	24	0.74 (0.04)	0.48 (0.04)	0.23 (0.04)
Age					
≤ 50	95 (11.57)	24	0.75 (0.04)	0.50 (0.05)	0.28 (0.05)
> 50	49 (12.24)	24	0.73 (0.06)	0.45 (0.07)	0.10 (0.05)
Sex					
Male	83 (15.67)	24	0.78 (0.05)	0.49 (0.06)	0.27 (0.05)
Female	61 (6.56)	24	0.68 (0.06)	0.47 (0.06)	0.17 (0.05)
Focus					
Bulbar	28 (10.71)	24	0.60 (0.09)	0.41 (0.10)	0.12 (0.07)
LMN*	46 (10.87)	32	0.89 (0.05)	0.63 (0.07)	0.25 (0.07)
Global	52 (13.46)	24	0.69 (0.07)	0.42 (0.07)	0.26 (0.07)

*LMN – lower motor neuron
**results recorded as: percentage (standard error)

complete data in Frames B and C, the minimum age is 20). A single indicator variable distinguishes between men and women and two indicator variables for global and bulbar permit arbitrary location effects for the three focus classes. The asymptotic likelihood ratio chi-square statistics given in the table are calculated by squaring the parameter estimates divided by its standard error. The asymptotic chi-square statistic corresponding to focus differences is calculated as $b^T C^{-1} b$, where b is the vector of maximum likelihood estimates and C is the estimated variance-covariance matrix for b[65] (p 61). This statistic does not depend on which two focus types are used to define the indicator variables.

From Frame A it is clear that a strong prognostic effect of age is indicated (p = 0.0007). Sex and focus of disease do not serve as prognostic indicators (respective p values > 0.05). In Frame B, results are shown for the same analysis on all 144 patients for whom age and sex data were available. Also considered is the possible interaction between age and sex. Age is the only variable that produces a significant prognostic effect (p = 0.0025). Frame C shows the results of the stepwise analysis, in which variables are entered in accordance with their prognostic importance. Age is the only variable that is retained (p = 0.0001). From these analyses, it is clear that age is the only significant prognostic variable for ALS patients in this study. This finding agrees with our earlier results in which each covariate was studied individually. In the proportional hazards analysis, the age variable is continuous, whereas age was dichotomized in the earlier analysis, resulting in the loss of much information. Hence, the value of age at onset as a prognostic variable appears to be stronger here.

Having identified age as the only important prognostic variable in our application, we investigated four accelerated time failure models, the exponential, Weibull, log-normal, and log-logistic (PROC LIFEREG, SAS, 1985). The log-normal distribution was found to provide the best fit according to several criteria. First, it yielded the highest maximized likelihood of all the competing

models. Second, an analysis of residuals showed that they followed the assumed distributional form, i.e., a normal distribution in $\log_e T$ (p > 0.05). Third, estimated survival probabilities obtained from the log-normal model correlated most highly (r = 0.98) with those obtained from the proportional hazards model. Using the log-normal as the baseline distribution, estimated probabilities for survival adjusted by age at onset were calculated. These estimated survival probabilities are displayed in Table 6. For example, the probability of survival at 36 months for a patient who developed ALS at age 30 is 63%, whereas a patient developing the disease at age 60 has a 30% probability of survival at 36 months.

DISCUSSION

The first description of ALS by Aran was based largely on the clinical observations of Duchenne.[1,2] Yet the distillation of ALS as a clinicopathological entity is attributed to Charcot.[5] Similarly, while familial cases of ALS were described by both Aran[1,2] and Bernhardt,[28] the concept of an inherited form of ALS did not gain acceptance until the later works of Kurland and Mulder, Engel et al, and Faveret.[17,18,21] The documentation of both familial clustering in the hyperendemic foci of ALS in the Western Pacific[67] and of several American pedigrees emphasized the distinctive nature of familial ALS.[21]

The last major comprehensive literature review of familial ALS delineated a primarily autosomal dominant mode of inheritance with an average age of onset of 46.8 years — rarely falling outside of 40 to 60 years.[18,68] The average survival was 30 months with the shortest being 9 months and the longest rarely more than 5 years. The authors made note of previously documented cases of exceptionally long survival but did not recognize these as unique. While only 19 families (84 cases) of verifiable ALS could be ascertained when the literature reports were
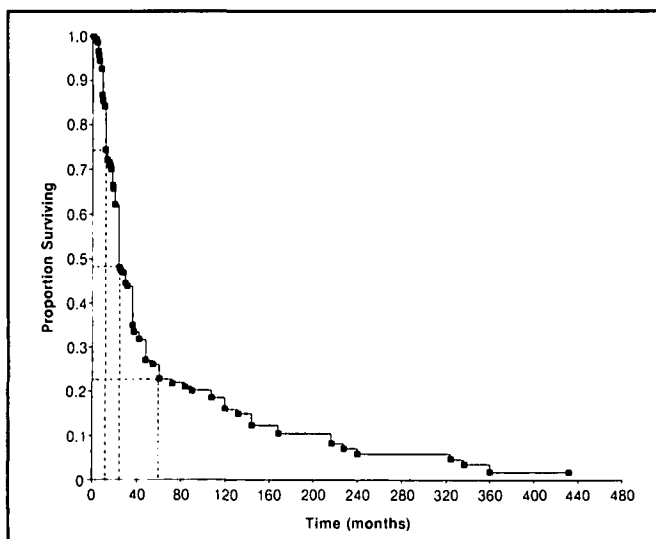

Figure 4 — The Kaplan-Meier survival curve for all familial ALS patients. The percentage surviving at 12, 24 and 60 months are indicated (dashed lines) and correspond approximately to the 25th, 50th and 75th percentiles, respectively.
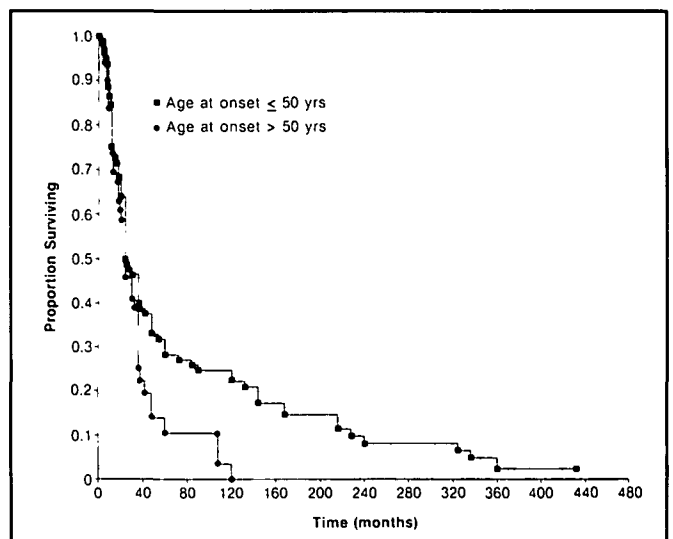

Figure 5 — The Kaplan-Meier survival curve for all familial ALS patients dichotomized at age 50. Survivorship is comparable between the two groups during the initial 24 months. However, by 60 months, distinct differences in the percentage surviving are apparent, a feature most striking after 120 months duration where no patients with disease onsetting at > 50 years of age are reported.

categorized according to the validity of the diagnosis, their final analysis contained 29 families (121 cases) — the authors ultimately having included less stringently defined cases for analysis. The majority of these latter families included only one verifiable case of ALS.

Inclusion Criteria

In this analysis, as in those of recent investigators, we have considered ALS as a clinically distinctive rather than generic disease of the motor neurons.[69] Therefore, we restricted the cases analyzed to those in which the presence of progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and pyramidal dysfunction could be unequivocally determined. Thus, although 100 families were found to have been reported as familial ALS or MND, ultimately only 53 pedigrees were determined to be sufficiently well documented to be considered for our analysis. Less stringent inclusion criteria would have embraced such diverse cases as 'long duration' chronic spinal muscular atrophy without bulbar or pyramidal dysfunction,[70] familial monomelic amyotrophy with hyperreflexia[71] or familial monomelic amyotrophy with hyporeflexia[72] — pedigrees of which have been included in earlier discussions of "familial ALS".

The inability to substantiate a familial diagnosis constituted a major category of exclusion and fell into two broad types. The first type was an inadequate case ascertainment as exemplified by the pedigree reported by Poser in which ALS was documented in the proband but the remaining cases were described only as having had "creeping paralysis" or "progressive muscle atrophy".[73] Several other families fell into this broad category of exclusion.[74-77] The second type consisted of those families in which ALS was well documented in the proband yet other family members suffered from PBP, PMA[78,79] or from such minor changes as hyporeflexia.[80] Occasional reports were encountered where the proband clearly suffered from ALS, yet the key related case suffered from an unrelated illness mistakenly described as ALS. Examples of such diverse conditions as cervical myelopathy,[81] progressive supranuclear palsy (ref 82 — case 2),

Table 5: Results of Fits of the Proportional Hazards Model to Familial ALS Data

Variable	Parameter Estimate	Standard Error	L.R. Chi-Square	p Value
Frame A: Focus data (n = 126)				
Age	0.0296	0.0087	11.63	0.0007*
Sex	0.1994	0.1991	1.05	0.3057
Focus			1.65	0.4382
Global vs LMN	0.0896	0.2199		
Bulbar vs LMN	0.3277	0.2578		
Frame B: Age and sex data (n = 144)				
Age	0.0314	0.0104	9.17	0.0025*
Sex	0.3379	0.7079	0.23	0.6331
Age × sex	−0.0037	0.0147	0.06	0.8031
Frame C: Age data (n = 144)				
Age	0.0306	0.0080	14.74	0.0001*

*significant beyond the 0.01 level

Table 6: Estimated Probability of Survival for Familial ALS Patients Based on Age at Onset of Disease.

Survival (months)	Age at Onset (years)										
	20	25	30	35	40	45	50	55	60	65	70
12	0.95	0.93	0.91	0.89	0.86	0.82	0.78	0.74	0.69	0.64	0.58
24	0.84	0.81	0.76	0.72	0.67	0.61	0.55	0.50	0.44	0.38	0.33
36	0.73	0.68	0.63	0.58	0.52	0.46	0.40	0.35	0.30	0.25	0.21
48	0.64	0.58	0.53	0.47	0.41	0.36	0.30	0.26	0.21	0.17	0.14
60	0.56	0.50	0.44	0.39	0.33	0.28	0.24	0.19	0.16	0.12	0.10
72	0.49	0.43	0.38	0.32	0.27	0.23	0.19	0.15	0.12	0.09	0.07
84	0.43	0.38	0.32	0.27	0.23	0.19	0.15	0.12	0.09	0.07	0.05
96	0.38	0.33	0.28	0.23	0.19	0.15	0.12	0.10	0.07	0.06	0.04
108	0.34	0.29	0.24	0.20	0.16	0.13	0.15	0.08	0.06	0.04	0.03
120	0.31	0.26	0.21	0.17	0.14	0.11	0.08	0.06	0.05	0.04	0.03
132	0.28	0.23	0.19	0.15	0.12	0.09	0.07	0.05	0.04	0.03	0.02
144	0.25	0.21	0.17	0.13	0.10	0.08	0.06	0.05	0.03	0.02	0.02
156	0.23	0.19	0.15	0.12	0.09	0.07	0.05	0.04	0.03	0.02	0.01
168	0.21	0.17	0.13	0.10	0.08	0.06	0.05	0.03	0.02	0.02	0.01
180	0.19	0.15	0.12	0.09	0.07	0.05	0.04	0.03	0.02	0.01	0.01
192	0.17	0.14	0.11	0.08	0.06	0.05	0.03	0.03	0.02	0.01	0.01
204	0.16	0.13	0.10	0.08	0.06	0.04	0.03	0.02	0.02	0.01	0.01
216	0.15	0.12	0.09	0.07	0.05	0.04	0.03	0.02	0.01	0.01	0.01
228	0.13	0.11	0.08	0.06	0.05	0.03	0.02	0.02	0.01	0.01	0.01
240	0.12	0.10	0.07	0.06	0.04	0.03	0.02	0.02	0.01	0.01	0
300	0.09	0.07	0.05	0.04	0.03	0.02	0.01	0.01	0.01	0	0

scapulohumeral dystrophy[83] and probable radiation myelopathy (ref 33 — Famille M. Bla., case II-7) were found. In some cases, no diagnosis was recorded.[33,84]

Rarely, as typified by the Farr family of Vermont, independent authors reported on successive generations of the same family. Initially described by Osler as a pedigree of PMA, this family was further expanded upon by Brown, and eventually described histologically by Powers.[85-87] While this latter report confirmed the diagnosis of ALS in a single case (accompanied by changes in the posterior columns and dorsal spinocerebellar tracts), the remainder of the pedigree did not meet the inclusion criteria.

Characteristics of Familial ALS

After the application of the categorical scores, 149 cases in 53 pedigrees remained in which we could be certain of the diagnosis. Taking this as our data base, several inferences could be drawn about the clinical characteristics of the disease. Firstly, in contrast to the age-related incidence of the sporadic form of ALS that indicates an increasing disease incidence with increasing age,[62,88] we find familial ALS patients, as a group, to be normally distributed about a mean age of onset of 45.7 years. This is virtually identical to the observations of others: 47.7 years,[21] 46.8 years,[18] 45.1 years.[10] The sex ratios (M:F) do not differ significantly from 1:1. The concomitant variables age at onset of disease, sex and disease focus are clearly unrelated variables, and of these, only the age at onset of disease was found to be a predictor of survival. In this regard, it is particularly significant that we have found no correlation between the clinical focus of disease onset and survival. Based on the analysis of the hyperendemic focus of ALS on the Kii Peninsula, one might have anticipated that long duration cases would typically have onset with PMA[89] — a feature which our data does not demonstrate.

The survival curve for familial ALS is markedly skewed. While the median survival for the population as a whole is 24 months, 23% of patients are still alive at 60 months. In common with survival data of sporadic ALS data, 26% of patients who developed ALS at less than age 50 survived to 60 months, whereas only 10% with onset at greater than age 50 survive at 60 months.[61,62] This analysis, however, contrasts with a recent analysis of familial MND in which the mean duration was demonstrated to be 11 months.[90] This analysis is not only at odds with this study, but also that of previous authors.[10,18] It is possible that a combination of several diseases of the motor neurons within one analysis may have introduced a bias towards more 'malignant' cases. A rapidly progressive form of familial ALS with death occurring within a year of disease onset has been well documented, (ref 18 — Famille 'NER', ref 21 — 'B family', 29, 33, 59, 91) leading us to have previously considered this a 'malignant' subgroup.[92] In this current analysis, we were unable to confirm the existence of this as a distinct subgroup. Families expressing a tendency towards a rapidly progressive form of ALS seem to be only a curiosity within the continuum of familial ALS.

Our demonstration of 23% of patients still surviving at 60 months is compatible with the notion of an exceptionally slowly evolving variant of familial ALS.[7,39,49] Horton et al have proposed that these cases might be considered as a distinct subpopulation of familial ALS.[7] A similar finding has been suggested

for sporadic ALS. In an extensive review of 515 cases of sporadic MND in Japan, Kondo and Hemmi demonstrated the existence of two subpopulations of ALS patients based on disease duration and suggested an improved prognosis in those patients surviving longer than 46 months.[93] However, in neither of these analyses was the relationship of age at onset to survival explored. As we have demonstrated, age at onset is a highly significant predictor of survival for familial ALS and should be treated as a covariable in the analysis of survival. Thus, it is not clear that the existence of long-term survival patients in the previous studies is not solely related to age of onset. This question is the subject of ongoing analyses.

By demonstrating that age at onset is the only clinical variable which impacts on survival, we were able to calculate survival probabilities based on the knowledge of age at onset (Table 6). We treated the data base as independent case reports to arrive at these survival probabilities, rather than as a collection of pedigrees. The importance of this is highlighted by the report of Chio et al, in which a significant interfamilial but not intrafamilial variability in the age of onset and survival within eight families with motor neuron diseases was documented.[94] Unfortunately, it is not clear that progressive bulbar palsy was present in all cases, making direct comparisons with our data questionable. Similarly, Williams et al have recently suggested that there may be significant underreporting of cases in familial ALS pedigrees.[95] Nonetheless, Chio's results do suggest that, in predicting the phenotypic expression of a given case, the antecedent family history must be heavily weighted. Although our retrospective analysis does not lend itself to this type of linkage analysis, there is a tendency towards an uniformity of disease duration within many of the pedigrees. One rarely finds exceptionally short-term survival within families where the predominant expression is a long-term survival. Within the long-term survival families, there is also a striking uniformity of survival. The exceptions to this are the families of Dierssen Gervas;[37] Espinosa, Okihiro, Mulder and Sayre;[41] Liberati and Pompi.[42] Even in these latter families, only single cases are expressed outside the family propensity. We suggest, therefore, that the application of Table 6 in a clinical setting be done in the context of a detailed family history. When the pedigree itself does not demonstrate a significant trend to either extremes of survival, survival estimates taken from Table 6 are likely to be of greater use.

Cases Excluded from the Final Analysis

A surprising number of case reports in the literature were excluded from our analysis. In reviewing these cases, it was apparent that ALS, PBP and PMA can form, in the adult population, a continuum of disease of the motor neuron within a pedigree and while they may be appropriately considered specific disease entities, they, nevertheless, likely bear a common clinicopathological thread. The earliest documentation of this continuum is the pedigree recorded by Hamilton in which two of four members were documented to have ALS, one had both PMA and pyramidal dysfunction without bulbar involvement and the final member had PMA and PBP without pyramidal disease.[29] A similar pedigree was described by both Montanaro and Lopez[96] and Thompsen and Alvarez.[97] This spectrum was confirmed histologically in the "B" Family of Engel, Kurland

and Klatzo[17] in which case IV-4 clinically and histologically had ALS, case IV-3 PMA but pathological evidence of pyramidal disease, case IV-2 PMA and PBP clinically (with additional pyramidal tract degeneration being found histologically; see ref 6) and III-1 flaccid atrophic weakness alone. In a more recently described family, three of five patients failed to express signs of pyramidal dysfunction and a fourth failed to express bulbar findings clinically or histologically while the proband clearly had ALS.[80] The most extensive collection of these illustrative pedigrees are those recorded by Horton, Eldridge and Brody (see ref 7 — families 1, 6, 8, 10, 11, 12 and 14).

The postulate that insufficient time had passed for full disease expression in such cases is refuted by the family of Houff, Calabrese and Taylor.[98] Here, while the propositus failed to manifest either clinical or histological evidence of pyramidal involvement in spite of a 22 year history, the afflicted mother fully expressed the disease. A similar scenario is described by Aydillo,[39] in which both ALS and PMA is demonstrated in the same family, all cases being of long duration. Instances of PMA and pyramidal dysfunction in the absence of bulbar disease have also been well documented (40 — 'B family', 49). We have found no cases of purely pyramidal dysfunction within these pedigrees — a finding analogous to that of other recent studies.[26]

Discerning whether this continuum, in fact, indicates a single gene defect with variable penetrance, one or more unrelated gene defects drawing on a limited phenotypic pool (giving the appearance of a continuum of diseases) or neither remains to be resolved.

Conclusions

We have utilized descriptive and exploratory statistical techniques to describe the clinical limits of familial ALS. We find that the age of onset is normally distributed about a mean age of 45.7 years, that the survival data is significantly skewed with a median survival of 24 months and 23% survival at 60 months. Age at onset was found to be the only predictor of survival, with younger age at onset predicting longer survival. There is no relationship between age at onset, sex or focus of disease at onset. It was also apparent from the literature that a spectrum of motor neuron disorders, encompassing ALS, progressive spinal muscular atrophy and progressive bulbar palsy can occur within the same pedigree, suggesting a common pathogenic mechanism. Studies are in progress to determine if these features serve to predict the neuropathological variant of the disease.

Appendix I

In our study, the proportional hazards model takes the following form

$$\log_e \left(\frac{h_i(t)}{h_0(t)} \right) = b_1 (x_1 - \bar{x}_1) + \ldots + b_p (x_p - \bar{x}_p) \qquad (3)$$

where $h_i(t)$ is the hazard function for the ith individual at survival time t, $h_0(t)$ is the hazard function when all patient characteristics (concomitant variable) are at their average value, the x's represent the concomitant variables (and their cross-product terms), and $\bar{x}$'s represent average values of patient characteristics (64 — sect 10.2, 99, 100 — sect 7.5). The regression coefficients were

calculated with the PHGLM procedure[101] — first by forcing all variables into the model and subsequently by using a stepwise procedure so that the first patient characteristic to enter the model was the single most important characteristic in predicting survival, the second variable was the second most important, etc. Generally speaking, the hazard function gives the risk of death per unit time so that variables in the equation that tend to increase the hazard function tend to decrease the time to death.

Cox's model (1972) provides a robust method for determining important prognostic factors. One reason is that it does not require specification of the form of the baseline hazard or survivor functions. However, if the baseline hazard and survivor functions can be specified, then accelerated failure time models may be used (65 — sect 2.3.3).

Accelerated failure models may be described by the general form

$$Y = \log_e T = \underline{x}' \, \underline{\beta} + PW \qquad (4)$$

where Y is the natural log of the survival time, $\underline{x}'$ is a vector of covariates, $\underline{\beta}$ is a vector of coefficients, P is a scaling parameter, and W is assumed to follow a specific error distribution. The effect of the prognostic variable(s) is to scale the baseline distribution of death times.

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