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Regional spread pattern predicts survival in patients with sporadic amyotrophic lateral sclerosis

G. M. Gargiulo-Monachelli[a,b], F. Janota[a], M. Bettini[a], C. L. Shoesmith[b], M. J. Strong[b] and R. E. P. Sica[c]

[a]*Department of Neurology, Ramos Mejia Hospital. School of Medicine, Buenos Aires University, Buenos Aires, Argentina;* [b]*Department of Clinical Neurological Sciences, University of Western Ontario, London, ON, Canada; and* [c]*Department of Science and Technology, School of Medicine, Buenos Aires University, Buenos Aires, Argentina*

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Background and purpose: Sporadic amyotrophic lateral sclerosis (sALS) is a disease with a focal clinical onset and contiguous spread. We examined patterns of disease spread following symptoms onset in sALS and whether the pattern of spread predicted survival.

Methods: Review of medical records (2003–2009) at London Ontario and Buenos Aires clinic cohorts retrieved 318 patients with sporadic sALS. According to patient self-report, we determined eight spread patterns: rostro-caudal, caudo-rostral, crossed, circular, superior interposed, middle interposed, inferior interposed and isolated. The variables studied were as follows: age, gender, sALS phenotypes, time from onset to diagnosis and time and direction of the spreading to the first region. Survival from symptoms onset was analysed by Kaplan–Meier, Tarone-Ware and Cox proportional hazards methods.

Results: The direction of first spread was horizontal in 33%, rostral to caudal in 32% and caudal to rostral in 21%, whereas spread to remote regions was observed in 14% of patients. Survival curves and 3- and 5-year survival rates favoured patients with an isolated and caudo-rostral pattern of spread compared to patients progressing to distant regions without involvement in the intervening region, or 'superior and inferior interposed patterns' (Tarone-Ware $P = 0.001$, $\chi^2 = 0.002$ and $\chi^2 = 0.006$, respectively). Factors affecting survival were gender, time to diagnosis, flail arm phenotype and age at diagnosis.

Conclusions: We have provided evidence that not all spread in ALS is contiguous and that the nature of symptom progression influences survival. Patients with sALS with 'interposed patterns' had a worse prognosis, whereas patients with caudo-rostral pattern fared better than the rest.

Introduction

Amyotrophic lateral sclerosis (ALS) is known as a disease with a uniquely focal clinical onset and a contiguous spread [1–3]. The spread appears to have preferential directionality rather than a random pattern of advance. Some studies suggest that there is a higher probability for clinical symptoms to evolve rostro-caudally [2,4], but they do not fully characterize other potential patterns of spread. The precise mechanisms of symptoms spread in ALS are not understood, and the potential linkage between upper motor neuron (UMN) and lower motor neuron (LMN) involvement in ALS has not yet been elucidated. The notion of which is the primary neuron affected (UMN or LMN) has also long been debated [5–9]. However, there is probably no valid hypothesis that accounts for all clinical scenarios, in that both anterograde 'dying-forward' degeneration originating in the primary motor cortex [7] and retrograde 'dying-back' degeneration starting in the LMNs [8,9] have been proposed to occur in ALS.

A post-mortem neuropathological study favours contiguous spread in LMNs in that the advancement of degeneration occurs in a graded manner radiating from the region of symptom onset, a proposal based on the finding of the most severe neuronal loss being in the region of onset [4]. However, an alternative hypothesis

Correspondence: Gisella M. Gargiulo-Monachelli, Instituto de Biología y Medicina Experimental, Obligado 2490, 1428 Buenos Aires, Argentina (tel.: +54 11 4783 2869 (ext 220); fax: +54 11 4786 2564; e-mail: gargiulo.gisella@ibyme.conicet.gov.ar).

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suggests that the degeneration of cortical and spinal motor neurons occurs independently of each other and argues against trans-synaptic progression. In favour of this, a neurophysiological study established that UMN and LMN dysfunction progressed with an independent time course [10], and two neuropathological studies found an absence of correlation between the density of spinal motor neurons and corticomotoneurons in the corresponding areas of the motor cortex [11,12].

In this work, we sought to determine anatomical patterns of spread from region of symptom onset as self-reported by the patients. We reviewed the clinical records from two different ALS outpatient clinic databases and classified patients into eight spread patterns based on the sequence of anatomical region involvement. We analysed clinical-demographic characteristics, described the direction and time of first spread and sought to determine whether survival could be predicted by the nature of the pattern of spread.

Patients and methods

Subjects and inclusion–exclusion criteria

We examined the medical records of patients with the diagnosis of probable or definite sporadic ALS (sALS) (El Escorial diagnostic criteria [13]) and for whom survival data were available from two multidisciplinary ALS clinics named the Department of Neurology at the Ramos Mejia hospital of Buenos Aires, Argentina (n = 215), and the Department of Clinical Neurological Sciences of London, Ontario, Canada (n = 250), between years 2003 and 2009. Regarding the Canadian Institution, 146 patients were randomly selected from 250 available charts. From a total of 361 medical records reviewed amongst the two databases, 318 patients met the inclusion criteria. Patients with a positive family history for ALS (with a known or unknown mutation for the disease), primary lateral sclerosis, clinically possible ALS, ALS with fronto-temporal dementia (ALS-FTD) or ALS dementia as per published criteria [14] and respiratory onset sALS patients were all excluded from the analysis. The study was approved by each Centre's ethics review board.

Phenotypes

Patients were categorized according to the site of onset into bulbar or spinal sALS, and according to phenotype into flail arm (FA), flail leg (FL) and progressive muscular atrophy (PMA). The definition for the FA syndrome was an LMN disorder of at least 12 months of duration that was characterized by progressive, predominantly proximal weakness and wasting of the upper limbs that could include pathologic reflexes at some point of the disease (not spasticity or clonus) [15]. The definition for the FL syndrome was an LMN disorder of at least 12 months of duration with predominantly distal weakness and wasting of the lower limbs that could also include pathologic reflexes (not spasticity or clonus) [15]. Patients presenting with a pure LMN syndrome in more than one region for at least 1 year, which did not correspond to the FA or FL definition, were classified as PMA. Phenotype features were extracted from the patient's history and physical examination at first and subsequent assessments.

Directionality of spread

We described four different initial directions of spread: horizontal, rostral to caudal, caudal to rostral and towards distant regions, regarding the site of origin of the disease. The first to the second region affected according to the patient's history was indicative of initial direction of spread. The direction of spread was considered to be horizontal when the first region spread consisted of cervical to cervical contralateral or lumbar to lumbar contralateral. Rostral to caudal direction of spread was defined as spread either from the bulbar region to the cervical region or from the cervical region to the lumbar region. Caudal to rostral spread was defined as spread either from the lumbar region to the cervical region or from the cervical to bulbar regions. Finally, we considered spread as being towards distant non-contiguous sites in instances of bulbar to lumbar region, or lumbar to bulbar region.

Spread patterns

The patients were categorized into eight different patterns of spread using self-reported symptomatic data. This included the date and site of symptoms onset, and the date and site of involvement of successive affected regions. When simultaneous symptoms were described, and they affected different regions, we considered that the first region that was stated by the patient was the first to be affected chronologically. In patients that had isolated involvement at first consultation, we considered the spread pattern after at least 1 year of follow-up. Clinically affected regions were considered as symptoms of either the UMN or LMN at: the bulbar, right cervical, left cervical, right lumbar or left lumbar levels.

We considered eight spread patterns from onset to diagnosis or to 1-year follow-up, according to the order of the affected regions: superior interposed, middle interposed, inferior interposed, circular, crossed, rostrocaudal, caudo-rostral and isolated (Table 1). Superior

Table 1 Spread pattern operational definitions

Spread pattern	Regions involved[a]
Superior interposed	Bulbar to lumbar to cervical
Middle interposed	Cervical to bulbar to lumbar or cervical to lumbar to bulbar
Inferior interposed	Lumbar to bulbar to cervical
Circular	Cervical to ipsilateral lumbar to contralateral lumbar then contralateral cervical
Crossed	Unilateral cervical to contralateral lumbar or viceversa
Rostro-caudal	Bulbar to cervical to lumbar
Caudo-rostral	Lumbar to cervical to bulbar
Isolated	Bulbar or cervical or lumbar

[a]Unless otherwise stated, cervical and lumbar regions are right- or left-sided.

interposed involved spread from the bulbar to the lumbar region with subsequent cervical region involvement. Middle interposed involved spread from the cervical region to the bulbar region followed by the lumbar, or from the cervical region to lumbar region followed by bulbar involvement. The inferior interposed pattern consisted of an initial lumbar presentation followed by spread to the bulbar region and then to the cervical region. The circular pattern of spread consisted of spread from the cervical region to the ipsilateral lumbar region, followed by spread to contralateral lumbar region and then to the contralateral cervical region. Spread could occur in either a clockwise or counter-clockwise manner. The crossed pattern of spread consisted of those patients in whom symptoms spread in a diagonal pattern either from the cervical or lumbar region to the contralateral lumbar or cervical region, respectively. The rostro-caudal spread pattern involved spread from the bulbar to the cervical and then lumbar regions, whilst the caudo-rostral spread pattern was the opposite. The use of the term 'isolated' implied that symptoms had remained in the bulbar, cervical or lumbar levels without evidence of spreading during the time from onset of symptoms until the 1-year follow-up.

Other definitions

The time between the development of functional involvement from the first affected region to the second was termed first region spread time (FRST). Survival time was considered from onset of symptoms to either death or tracheostomy or censoring date of 31 December 2009. The date of death was ascertained by clinical records or telephone calls to patient's relatives. The 'time onset to diagnosis' was the time in months from symptoms onset as reported by the patient, spouse or other relative, to the time of diagnosis.

Statistical analysis

Clinical and demographic variables were compared between spread patterns using one-way analysis of variance for continuous variables with subsequent post hoc Bonferroni tests. Assumptions were tested by inspection of normality of the distribution by the Kolmogorov–Smirnov test and for homogeneity of variance by the Levene test. Variables that were non-normally distributed were normalized by log transformation as in survival, FRST and time onset to diagnosis. Categorical variables were compared using the chi-square test. Survival times were analysed using the Kaplan–Meier method, and survival curves between groups were compared using the Tarone-Ware test. Censoring date for survival data was 31 December 2009. The Cox proportional hazards model with the forward Wald method was used to assess the simultaneous effects of several independent variables on survival and to obtain adjusted survival curves. Significance was tested at the 5% level, and all the analyses were performed using R-project [16].

Results

We obtained a total of 318 patients between the two cohorts of which 282 (89.5%) patients were classified according to spread patterns and 36 were excluded for insufficient data. Survival data were complete for the Kaplan–Meier analysis for 226 (71%) cases. The proportion of patients alive at censoring was 28.8%. A comparison of demographic and clinical characteristics of the Buenos Aires patients, the London patients and the combined cohort is described in Table 2.

The most frequent directionality of initial spread included either to an adjacent horizontal region (i.e. from one limb to the contralateral limb) as observed in 33% of patients or to contiguous rostral to caudal regions (i.e. from one region to the more caudal one) in 32% of patients. A smaller percentage of patients demonstrated a caudal to rostral direction with 21%, and towards distant non-contiguous sites in 14% of the patients analysed.

Of the 282 patients in the spread pattern classification, 17% had rostro-caudal, 17% had middle interposed, 13% had crossed, 10% had caudo-rostral, 9% had circular, 9% had isolated, 7.8% had superior interposed and 7% had inferior interposed. For complete data on frequency, gender, age at diagnosis, time onset to diagnosis, FRST and survival time for the different spread pattern groups, see Table 3. Gender amongst spread patterns showed a 1.2- to 3.1-fold male predominance in all cases except the rostro-caudal pattern patients (M:F ratio 0.8:1). This is understandable

Table 2 Demographic and clinical characteristics of the Buenos Aires, London and combined databases

	Buenos Aires patients	London patients	Combined data
Total *N*	215	103	318
Gender *n* (%)			
Masculine	135	63	198
Feminine	80	40	120
M/F Ratio	1.7:1	1.5:1	1.6:1
Age at diagnosis (years)			
Mean	55	61	57
Median (range)	57 (22–79)	61 (27–87)	58 (22–87)
Time to diagnosis (months)			
Mean	20.5	18.6	19.9
Median (range)	16 (1–84)	13 (3–120)	14 (1–120)
First region spread time (months)			
Mean	7.1	12.4	9.1
Median (range)	5 (0–36)	7 (1–90)	6 (0–90)
Phenotypes *n* (%)			
Bulbar	43 (24)	37 (36)	80 (29)
Spinal	113 (64)	55 (53)	168 (60)
Flail arm	10 (6)	6 (6)	16 (6)
Flail leg	5 (3)	3 (3)	8 (3)
PMA	6 (3)	2 (2)	8 (3)
Survival (months)			
Mean	42.4	41.4	41.8
Median (range)	36 (7–163)	31 (9–170)	35 (7–170)
3-year survival rate (%)			
Superior interposed	14	18	17
Inferior interposed	25	43	32
Crossed	58	43	55
Circular	50	33	45
Rostro-caudal	45.5	22	33
Caudo-rostral	54.5	53	54
Middle interposed	52	67	57
Isolated	50	73	61
5-year survival rate (%)			
Superior interposed	14	0	6
Inferior interposed	0	29	10.5
Crossed	21	29	22
Circular	12.5	33	18
Rostro-caudal	18	9	13
Caudo-rostral	45.5	27	35
Middle interposed	29.6	20	26
Isolated	25	36	30

PMA, progressive muscular atrophy.

because, by our definition, all rostro-caudal patients would have had a bulbar symptom onset and, thus, a greater likelihood of being of female gender [17]. There were no significant differences between the mean age at diagnosis, time onset to diagnosis and survival amongst the individual spread patterns based on the Bonferroni analysis. FRST showed significance in that the isolated pattern and the inferior interposed pattern subgroups were different ($P = 0.03$). The inferior interposed pattern had the shortest median (mean ± SE) time, with 4 (6.7 ± 1.7) months, whilst the isolated pattern subgroup had the longest time to spreading with 11 (15 ± 3.1) months.

The overall median survival in the cohort was 35 months, ranging between 7 and 170 months. The longest median survivals by Kaplan–Meier analysis were observed in the isolated pattern (53 months) and caudo-rostral pattern patients (61 months), whilst the shortest survivals were observed in the inferior interposed (28 months) and superior interposed (23 months) pattern patients. Three- and 5-year survival rates were also lower in superior and inferior interposed patterns compared to isolated and caudo-rostral pattern patients (3-year survival rate: $\chi^2 = 0.002$ and 5-year survival rate: $\chi^2 = 0.006$). For complete information on survival rates of both cohorts and the combined data, see Table 2. The Kaplan–Meier survival curves for the eight spread pattern subgroups were different overall (Tarone-Ware $\chi^2 = 25.1$; $P = 0.001$), suggesting the nature of the symptom progression influences survival, being survival curves for superior and inferior interposed patterns the worst and caudo-rostral and isolated patterns the best regarding prognosis, as shown in Fig. 1a.

For the Cox proportional hazards method, we analysed the same variables as in the separate analysis and obtained adjusted survival curves at the covariate means (Model $\chi^2 = 101.7$, d.f. = 4, $P < 0.001$). As described in the earlier analysis, patients with caudo-rostral and isolated patterns had the best survival whilst superior and inferior interposed pattern patients presented the shortest survival time (Fig. 1b). Factors independently affecting survival within the model were time to diagnosis, age at diagnosis, gender and FA phenotype, entering the equation in that order with the forward Wald method (Table 4). Using the variable of 'time to diagnosis', the hazard of death is reduced by 7% for each month that the patient's time to diagnosis was above the mean value (HR = 0.93, 95% CI = 0.91–0.95, $P < 0.001$). For each year the patient's age at diagnosis was above the mean, the hazard was increased by 3.6%. (HR = 1.03, 95% CI = 1.02–1.05, $P < 0.001$). Male gender increased the hazard by two-fold compared to female gender (HR = 2.15, 95% CI = 1.45–3.19, $P < 0.001$) and having the FA phenotype reduced the hazard by 83% (HR = 0.17, 95% CI = 0.04–0.6, $P = 0.006$). The remaining phenotypes and FRST were not significant factors affecting survival. However, the time to spread to a second region (or FRST) correlated positively with survival time in the combined cohort (Pearson $r = 0.45$; $P < 0.001$).

Discussion

In this study, we have provided evidence that not all patterns of spread in sALS are contiguous, based on our observation of initial directionality to distant, non-

Table 3 Demographic and clinical characteristics of spread patterns

	Rostro-caudal	Caudo-rostral	Circular	Crossed	Superior interposed	Middle interposed	Inferior interposed	Isolated	*P*
Total *N* (%)	55 (17)	32 (10)	29 (9)	41 (13)	22 (7.8)	54 (17)	20 (7)	29 (9)	
Gender *n* (%)									
Masculine	25 (45.5)	20 (62.5)	22 (76)	25 (61)	12 (54.5)	40 (74)	12 (60)	20 (69)	0.06*
Feminine	30 (54.5)	12 (37.5)	7 (24)	16 (39)	10 (45.5)	14 (26)	8 (40)	9 (31)	
M/F Ratio	0.8:1	1.6:1	3.1:1	1.5:1	1.2:1	2.8:1	1.5:1	2.2:1	
Age at diagnosis (years)									
Median (range) mean ± SE	61 (22–84)	57 (25–83)	54 (38–76)	55 (34–79)	60.5 (48–87)	56 (30–86)	61.5 (47–79)	63 (35–86)	0.02**
	59 ± 1.8	55 ± 2.8	55 ± 1.9	54 ± 1.8	62 ± 2.3	55 ± 1.8	62 ± 2	61 ± 2.3	
Time to diagnosis (months)									
Median (range) mean ± SE	12 (1–60)	15 (4–84)	10 (4–96)	21 (3–64)	11 (5–53)	17 (4–120)	24 (6–37)	12 (4–48)	0.03**
	16 ± 1.9	22 ± 3.5	18 ± 4.2	21 ± 1.9	15 ± 2.5	24 ± 2.9	22 ± 2.5	16.5 ± 2.1	
Survival (months)[a]									
Median (95% CI) mean ± SE	31 (23–39)	61 (33–89)	36 (28–44)	41 (30–52)	23 (18–28)	48 (34–62)	28 (17–39)	53 (19–87)	0.01**
	46 ± 7	72 ± 12	54 ± 11	48 ± 5	38 ± 9	65 ± 9	35 ± 5	62 ± 7	
FRST (months)									
Median (range) mean ± SE	6 (1–35)	8 (1–36)	5 (1–90)	5 (1–24)	6 (1–31)	6 (1–72)	4 (1–24)	11 (0–65)	0.01**
	9 ± 1.1	11 ± 1.8	8 ± 3	7 ± 1	8 ± 1.6	9 ± 1.5	7 ± 1.7[b]	15 ± 3.1[b]	

*Chi-square test; **One-way analysis of variance with post hoc Bonferroni test; [a]Survival data as per Kaplan–Meier analysis; [b]By Bonferroni test, only FRST showed isolated pattern and inferior interposed pattern subgroups were different ($P = 0.03$); FRST, first region spread time; CI, confidence interval; SE, standard error.

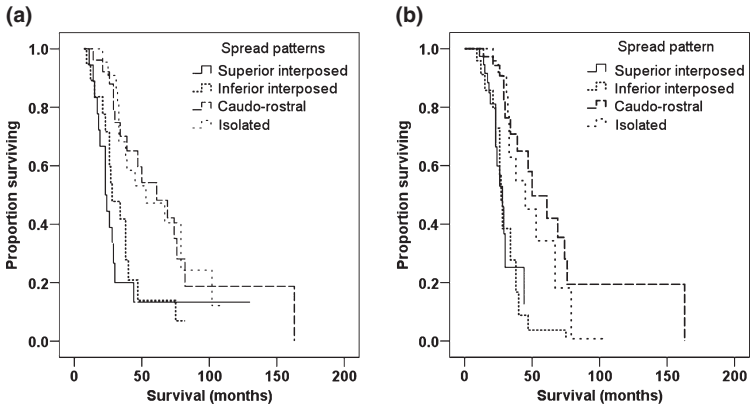

Figure 1 Survival curves for superior and inferior interposed, isolated and caudo-rostral spread patterns in the combined population. (a) Kaplan–Meier survival curves for superior and inferior interposed, isolated and caudo-rostral spread patterns. Tarone-Ware $\chi^2 = 25.1$; $P = 0.001$. (b) Survival curves for superior and inferior interposed, isolated and caudo-rostral spread patterns after adjusting for time onset to diagnosis, age at onset, gender, phenotypes and first region spread time at the covariate means using Cox regression model ($\chi^2 = 101.7$, d.f. $= 4$, $P < 0.001$).

Table 4 Cox proportional hazards model in the combined analysis

Variable	HR	95% CI	*P*
Time onset to diagnosis (months)	0.93	0.91–0.95	< 0.001
Age (years)	1.03	1.02–1.05	< 0.001
Male gender	2.15	1.45–3.19	< 0.001
Phenotypes:			
FA	0.17	0.04–0.6	0.006
Spinal	0.86		0.35
Bulbar	0.52		0.47
FL	0.28		0.59
PMA	0.06		0.80
First region spread time (months)	0.34		0.55

Time onset to diagnosis, age at diagnosis, gender and flail arm phenotype remain independently significant prognostic factors. First region spread time and spinal, bulbar, flail leg and PMA phenotypes are not independently significant factors; FA, flail arm; FL, flail leg; PMA, progressive muscular atrophy; CI, confidence interval; HR, hazards ratio.

adjacent, regions and of 'interposed patterns' of spread in a significant proportion of patients. In these patients, accounting for 14% of all patients with sALS, we observed an initial directionality towards distant sites, and for less than 8% of the sample population, we found spread to be from bulbar to lumbar regions or vice versa, with subsequent involvement of the cervical region. The most common direction of spread was to adjacent regions, a feature similar to that observed by others [2–5,18]. However, we have further shown that this most frequent initial spread had a horizontal and rostral to caudal directionality, suggesting that the underlying motor neuron degeneration had preferential directions of spread rather than simple radial or centrifugal directions. The term 'middle interposed' is, in fact, a contiguous pattern because it spreads from the cervical region to the bulbar or from the cervical to the lumbar regions. If we consider our findings of interposed spread, they could suggest that the degeneration of either the UMN or LMN gives rise to topographically separated symptoms because intermediate regions – perhaps affected – are less or not at all noticed symptomatically by the patients; alternatively, the degeneration of either motor neuron could be localized independently from each other in the neuraxis.

Our observation of non-contiguous clinical progression of the disease has also been described by others regarding independent UMN and LMN spread after onset. The UMN/LMN spread was previously addressed by means of electrophysiological studies which concluded that in the early stages of the disease there was a link between UMN and LMN dysfunction, disappearing after disease onset when degeneration of motor neurons probably becomes independent [10,19]. Ravits *et al.* [5] have suggested that UMN/LMN signs derived from physical examination were maximal at the same body region of onset, but during disease progression the UMN and LMN involvements were independent of each other, either in different body regions or in the same body region but to different extents. The explanation advanced by those authors was that the disease progression followed the somatotopically arranged neuronal anatomy for both motor neurons. Nonetheless, a post-mortem study by the same authors found that 68% of their patients had the greatest loss of LMNs closer to the region of clinical onset; but interestingly, they also found that 44% of their patients showed greater loss of neurons in areas

different from the region of onset, showing remarkable coincidence with our clinical findings of interposed spread [4]. Körner *et al*. [18] also found that clinical LMN involvement was, soon after the disease onset and during further progression, more frequent in the region of onset. In contrast, they observed that the frequency of UMN signs was independent of the onset region and was higher in the lumbar region at any given time. They also documented degeneration of motor neurons in non-adjacent regions in some patients with sALS and assumed that multifocal disease onset might occur in those patients [18].

In reference to survival, the superior and inferior interposed patterns had a significantly worse prognosis in terms of median, Cox-adjusted survival curves and 3- and 5-year survival rates compared to patients with caudo-rostral and isolated spread. Patients progressing caudo-rostrally can be expected to fare better because the onset is far away from sites more related to muscle function devoted to breathing and swallowing, such as the cervical and bulbar regions, thus rendering a longer survival for patients starting in lumbar regions that, lately, progress rostrally. Similarly, the isolated pattern includes patients with FA and FL phenotypes, because their disease remained isolated to one region for at least 1 year. Certainly, this may be the reason why isolated pattern patients had a higher median survival in months and a higher 3- and 5-year survival rates. Albeit this concept appears to be understandable, the reason for the increased mortality in the interposed spread subgroups remains unclear. We do not know the mechanisms that could underlie this type of non-contiguous spread that account for the poorer outcome in these patients, perhaps the almost simultaneous starting of the disease at two different points of the neuraxis might be at the base of this behaviour.

After adjusting for independent variables, only time onset to diagnosis, age at diagnosis, gender and FA phenotype were significant predictors of survival. Higher age at diagnosis is widely recognized as a worse prognostic factor, and population-based studies have already shown its influence on survival [20,21]. There is controversy whether gender influences prognosis. Although in some studies gender appears to have no clear effect on survival [17,20], we observed that male gender independently influenced survival (Cox analysis). We also confirmed that an FA presentation confers a better prognosis, consistent with published reports [15]. Although FRST was not an independent factor influencing survival in the Cox method, it had a positive correlation with survival time. Others have previously shown a significant correlation between time to spread to a second region and survival for ALS phenotypes [15,22]. Moreover, FRST was different between spread patterns, with inferior interposed having the shortest and isolated pattern the longest time to spread. Indeed, this time was also longer in FA and FL cases [15], which is equivalent to our finding of longer FRST in the isolated pattern subgroup.

Patients with clinically possible sALS according to the El Escorial criteria were excluded owing to 37% of false negatives, as opposed to 4% with definite or probable diagnostic probability [23]. All cases with familial ALS (SOD1 and non-SOD1) were also excluded because of possibly distinct pathogenic mechanisms from patients with sALS [24]. In our study, we assessed regional spread patterns, not taking into account either UMN/LMN components or electrophysiological data, but according to the patient's history. This may have biased our search into LMN involvement, because UMN signs are less discernible symptoms for patients to manifest. However, we encountered many symptoms described by the patients that were later confirmed to be of UMN nature in the light of the physical examination. Another limitation of our study is its retrospective design. In the future, larger prospective studies comprising detailed information of UMN and LMN behaviour, clinical electrophysiology, along with regional patterns of spread, will be required to further validate and reproduce our conclusions.

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Disclosure of conflict of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Gowers WR. *Manual of Diseases of the Nervous System*. London: Churchill, 1886–1888 (reprinted special edition, Birmingham, AL: Classics of Medicine Library, 1981).
2. Brooks BR. The role of axonal transport in neurodegenerative disease spread: a meta-analysis of experimental and clinical poliomyelitis compares with amyotrophic lateral sclerosis. *Can J Neurol Sci* 1991; **18:** 435–438.

3. Ravits J, La Spada A. ALS motor phenotype heterogeneity, focality and spread. *Neurology* 2009; **73:** 805–811.
4. Ravits J, Laurie P, Fan Y, Moore DH. Implications of ALS focality: rostral-caudal distribution of lower motor neuron loss postmortem. *Neurology* 2007; **68:** 1576–1582.
5. Ravits J, Paul P, Jorg C. Focality of upper and lower motor neuron degeneration at the clinical onset of ALS. *Neurology* 2007; **68:** 1571–1575.
6. Charcot JM. Sclérose latérale amyotrophique. In: *Oeuvres Completes*, Vol. 2. Paris: Bureaux du Progres Medical; 1897: 249–266.
7. Eisen A, Kim S, Pant B. Amyotrophic lateral sclerosis (ALS): a phylogenetic disease of the corticomotorneuron? *Muscle Nerve* 1992; **15:** 219–224.
8. Chou SM, Norris FH. Amyotrophic lateral sclerosis: lower motor neuron disease spreading to upper motor neurons. *Muscle Nerve* 1993; **9:** 864–869.
9. Fischer LR, Culver DG, Tennant P, *et al*. Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. *Exp Neurol* 2004; **185:** 232–240.
10. Attarian S, Vedel JP, Pouget J, Schmied A. Progression of cortical and spinal dysfunctions over time in amyotrophic lateral sclerosis. *Muscle Nerve* 2008; **37:** 364–375.
11. Kiernan JA, Hudson AJ. Changes in sizes of cortical and lower motor neurons in amyotrophic lateral sclerosis. *Brain* 1991; **114:** 843–853.
12. Pamphlett R, Kril J, Hng TM. Motor neuron disease: a primary disorder of corticomotoneurons? *Muscle Nerve* 1995; **18:** 314–318.
13. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000; **1:** 293–299.
14. Strong MJ, Grace GM, Freedman M, *et al*. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009; **10:** 131–146.
15. Wijesekera LC, Mathers S, Talman P, *et al*. Natural history and clinical features of the flail arm and flail leg ALS variants. *Neurology* 2009; **72:** 1087–1094.
16. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2011. ISBN 3-900051-07-0, http://www.R-project.org/ (accessed 22/06/2011)
17. McCombe PA, Henderson RD. Effects of gender in amyotrophic lateral sclerosis. *Gend Med* 2010; **7:** 557–570.
18. Körner S, Kollewe K, Fahlbusch M, *et al*. Onset and spreading patterns of upper and lower motor neuron symptoms in amyotrophic lateral sclerosis. *Muscle Nerve* 2011; **43:** 636–642.
19. Attarian S, Vedel JP, Pouget J, Schmied A. Cortical versus spinal dysfunction in amyotrophic lateral sclerosis. *Muscle Nerve* 2006; **33:** 677–690.
20. Chiò A, Logroscino G, Hardiman O, *et al*. Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler* 2009; **10:** 310–323.
21. Chiò A, Mora G, Leone M, *et al*. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002; **59:** 99–103.
22. Turner M, Brockington A, Scaber J, *et al*. Pattern of spread and prognosis in lower limb-onset ALS. *Amyotroph Lateral Scler* 2010; **11:** 369–373.
23. Douglass CP, Kandler RH, Shaw PJ, McDermott CJ. An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease. *J Neurol Neurosurg Psychiatry* 2010; **81:** 646–649.
24. Zhai H, Bigio EH, Yan J, *et al*. FUS-immunoreactive inclusions are a common feature in sporadic and non-SOD1 familial amyotrophic lateral sclerosis. *Ann Neurol* 2010; **67:** 739–748.