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A proposed staging system for amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis is a neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons, with a median survival of 2–3 years. Although various phenotypic and research diagnostic classification systems exist and several prognostic models have been generated, there is no staging system. Staging criteria for amyotrophic lateral sclerosis would help to provide a universal and objective measure of disease progression with benefits for patient care, resource allocation, research classifications and clinical trial design. We therefore sought to define easily identified clinical milestones that could be shown to occur at specific points in the disease course, reflect disease progression and impact prognosis and treatment. A tertiary referral centre clinical database was analysed, consisting of 1471 patients with amyotrophic lateral sclerosis seen between 1993 and 2007. Milestones were defined as symptom onset (functional involvement by weakness, wasting, spasticity, dysarthria or dysphagia of one central nervous system region defined as bulbar, upper limb, lower limb or diaphragmatic), diagnosis, functional involvement of a second region, functional involvement of a third region, needing gastrostomy and non-invasive ventilation. Milestone timings were standardized as proportions of time elapsed through the disease course using information from patients who had died by dividing time to a milestone by disease duration. Milestones occurred at predictable proportions of the disease course. Diagnosis occurred at 35% through the disease course, involvement of a second region at 38%, a third region at 61%, need for gastrostomy at 77% and need for non-invasive ventilation at 80%. We therefore propose a simple staging system for amyotrophic lateral sclerosis. Stage 1: symptom onset (involvement of first region); Stage 2A: diagnosis; Stage 2B: involvement of second region; Stage 3: involvement of third region; Stage 4A: need for gastrostomy; and Stage 4B: need for non-invasive ventilation. Validation of this staging system will require further studies in other populations, in population registers and in other clinic databases. The standardized times to milestones may well vary between different studies and populations, although the stages themselves and their meanings are likely to remain unchanged.

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Abbreviation: ALS = amyotrophic lateral sclerosis

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons, with a median survival of 2–3 years (Kiernan *et al.*, 2011). Although various phenotypic and research diagnostic classification systems exist and several prognostic models have been generated, there is no staging system. For example, the El Escorial criteria (Brooks, 1994) and their subsequent derivatives use the relative burden of upper and lower motor neuron signs for classification of the clinical certainty of the diagnosis of ALS, but it is possible to have advanced disease and a less certain El Escorial category, and the criteria cannot therefore be used for staging.

Staging criteria are usually simple and define clinical milestones in the course of a disease that reflect severity, prognosis and options for treatment. Although the ALS Functional Rating Scale measures severity of disability as defined by function and prognosis, the monitored events cannot be regarded as simple staging milestones because many different modalities are assessed and it is really a disability scale producing a single aggregate score that correlates with functional progression (Group TAPI-IS, 1996; Cedarbaum *et al.*, 1999).

Similarly, there have been many models of ALS that use clinical factors at presentation for phenotypic classification and prediction of survival, but these are not staging criteria as there are no milestones (Boman and Meurman, 1967; Mulder and Howard, 1976; Mortara *et al.*, 1984; Ganesalingam *et al.*, 2009; Turner *et al.*, 2009).

Staging criteria for ALS would help to provide a universal and objective measure of disease progression with benefits for patient care, resource allocation, research classifications and clinical trial design. We therefore sought to identify clinical milestones that could be shown to occur at specific points in the disease course, reflect disease progression and impact prognosis and treatment. Such milestones could then form the basis of a staging system for ALS.

Materials and methods

Patient selection

The study had ethical approval from the institutional Research Ethics Committee (SLAM/IOP 222/02) and patients were included after informed written consent. A tertiary referral centre clinical database consisting of patients with ALS seen between 1993 and 2007 was analysed. The diagnosis was made by the referring neurologist or at the tertiary centre after full investigation to exclude other conditions. All patients met the revised El Escorial-Arlie House Criteria (Brooks *et al.*, 2000) for ALS, and also included those with pure lower and upper motor neuron syndromes. For patients seen before 2002, the El Escorial category was reclassified retrospectively. Patients with clinically obvious dementia at onset were excluded.

Methods and definitions

Patients were classified as having limb, bulbar or diaphragmatic onset ALS. For the purposes of analysis, those with diaphragmatic onset were classified with those with limb onset because of the common spinal basis of lower motor neuron degeneration. ALS milestones for investigation as potential staging criteria were selected on the basis of being easily clinically available by being routinely collected at any clinical visit, straightforward to define in terms of presence or absence of involvement, and useful for phenotypic classification (Wijesekera *et al.*, 2009). Milestones were defined as symptom onset (functional involvement by weakness, wasting, spasticity, dysarthria or dysphagia of one CNS region defined as bulbar, upper limb, lower limb or diaphragmatic), diagnosis, functional involvement of a second region, functional involvement of a third region, needing gastrostomy and non-invasive ventilation. As wasting was almost always associated with weakness, and for patients with ALS spasticity manifests as weakness, we did not differentiate between those patients whose onset was not weakness, but rather spasticity or wasting without weakness. Timing of involvement was based on the date of onset of symptoms and dates of development of functionally significant symptoms in a second and third region, which were gathered from the clinical history. Diagnosis was defined as a confirmed diagnosis of ALS made either by the referring neurologist or at the tertiary centre, as recorded in the case records. The need for gastrostomy was defined as the time gastrostomy or nasogastric feeding was provided or refused. The need for non-invasive ventilation was defined as the time non-invasive ventilation was provided, trialled or refused.

Milestone timings were standardized as proportions of time elapsed through the disease course using information from patients who had died by dividing time to a milestone by disease duration, a similar method to that used in a previous study of timings of medical interventions (Bromberg *et al.*, 2010). Thus the time to each milestone was a value between 0 and 1, with 0 being symptom onset and 1 being death. Date of death was ascertained by clinic records, death certificates and contact with the patient's registered general practitioner. The highest milestone recorded at last follow-up was used. Riluzole use was also recorded and defined as any use longer than 2 weeks.

Statistical analysis

Variables were expressed as mean [95% confidence interval (CI)]. Standardized times were compared by Student's *t*-test for two groups and one-way analysis of variance (ANOVA) for three or more groups, with subsequent *post-hoc* Dunnett tests. Variables that were non-normally distributed were normalized by log transformation. Non-parametric tests were used if transformation did not result in normality. Survival analysis was by Kaplan–Meier product limit distribution, with survival measured from clinical milestone to death or censor date. Analyses were performed in SPSS v17.0 (SPSS Inc).

Model validation

Construct validity (Smith, 2005) was tested by using the system to examine survival in the entire cohort, looking at median survival and 5-year survival in those with limb onset and bulbar onset ALS.

Results

Patient characteristics

There were 1471 patients with ALS. Twelve were excluded on the basis of cognitive impairment. Of the remaining 1459, 371 (25.4%) had bulbar onset ALS, 1088 (74.6%) had limb onset ALS and none had diaphragmatic onset. There were 892 males (61.2%) and 577 females (38.8%), with a male-to-female ratio of 1.9 in those with limb onset and 0.9 in those with bulbar onset. Mean age at onset was 57.4 years (95% CI 56.8–58.07). By Kaplan–Meier analysis, the median survival was 42.3 months (95% CI 39.8–45.0, range 4–274) for the entire population. The median survival was 48.3 months (95% CI 45.0–51.7, range 4–274) for those with limb onset and 30.8 months (95% CI 28.5–33.0, range 6–261) for those with bulbar onset. One thousand and sixty-seven patients had died at the end of follow-up, 295 with bulbar onset and 772 with limb onset. There was complete information for 1061 patients. Of the remainder, 238 were alive at the end of the study and could not therefore have milestones calculated as a proportion of disease duration, and 160 patients had been lost to follow-up.

The characteristics of the patients who had died were different from those not included in subsequent analysis because they were either still alive or had been lost to follow-up. Median age of onset was 60 years for those who had died, 54 years for those alive and 56 years for those lost to follow-up. Median diagnostic delay was 11 months for those who had died, 16 months for those alive and 15 months for those lost to follow-up.

Times to each milestone

Mean duration and standardized time from onset to every clinical milestone is given in Table 1 and displayed graphically in Fig. 1. Most patients had passed >1 milestone; we could therefore either analyse the timing of the last milestone reached or the timing of every milestone reached. Here, we report only the results of using the last milestone recorded for each patient, but using every available milestone from each patient does not substantially alter any of the results (Table 1).

Although milestones were reached at relatively predictable times, some tended to occur at similar time points to each other (Fig. 1, Tables 1 and 2). For example, the time to diagnosis was not particularly different from the time that a second region became weak.

Interestingly, the need for gastrostomy did not seem to occur at a different time from the need for respiratory support, but because the ease of diagnosis and the timing of subsequent spread could be different for those with bulbar and limb onset, we examined whether milestones were reached at different times in these groups (Table 2). We found gastrostomy was needed before non-invasive ventilation for patients with bulbar onset, but after

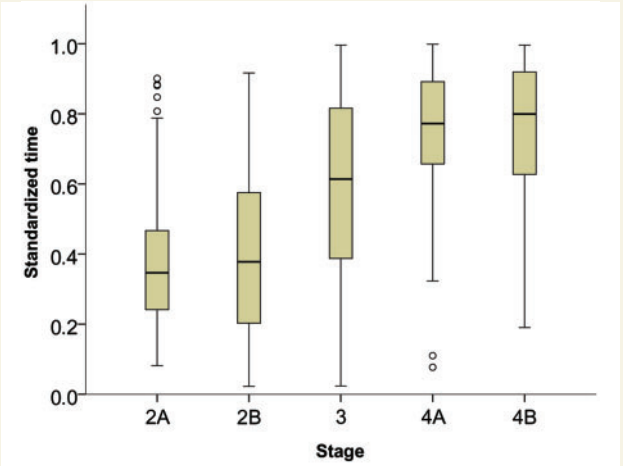

Figure 1 Boxplot showing standardized times to last recorded milestone (where 0 is onset of disease and 1 is death) for each stage in the entire cohort with ALS. Stage 1 (onset) is not explicitly shown but occurs at the origin; 2A = diagnosis; 2B = second region involved; 3 = third region involved; 4A = gastrostomy needed; 4B = respiratory support (non-invasive ventilation) needed. The line marks the median with the shaded box showing the interquartile range.

Table 1 Time taken to reach each milestone in patients who had died

	n	Mean milestone timing (months)	Standardized mean	Standardized median
Last recorded milestone				
Diagnosis	87	13.5 (11.3–15.7)	0.37 (0.33–0.42)	0.35 (0.24–0.47)
Involvement of second region	283	17.7 (15.5–19.8)	0.40 (0.37–0.42)	0.38 (0.20–0.58)
Involvement of third region	356	23.3 (20.8–25.7)	0.59 (0.57–0.62)	0.61 (0.39–0.82)
Need for gastrostomy	207	27.7 (25.1–30.2)	0.76 (0.73–0.78)	0.77 (0.65–0.90)
Need for non-invasive ventilation	134	30.3 (26.4–34.2)	0.75 (0.72–0.79)	0.80 (0.63–0.92)
Every milestone				
Diagnosis	1061	15.2 (14.3–16.1)	0.41 (0.39–0.42)	0.38 (0.24–0.55)
Involvement of second region	958	14.7 (13.6–15.8)	0.35 (0.34–0.37)	0.32 (0.14–0.53)
Involvement of third region	609	22.8 (21.1–24.5)	0.58 (0.56–0.60)	0.60 (0.37–0.80)
Need for gastrostomy	232	27.3 (25.0–29.7)	0.76 (0.73–0.78)	0.77 (0.65–0.90)
Need for non-invasive ventilation	163	31.5 (27.8–35.1)	0.76 (0.73–0.79)	0.80 (0.65–0.92)

Means are given with 95% CI of the mean in brackets. The standardized median is given with the interquartile range of the sample in brackets.

Table 2 Standardized times to milestones in patients with bulbar and limb onset ALS

Last recorded milestone	Bulbar onset ALS		Limb onset ALS	
	n	Milestone timing	*n*	Milestone timing
Diagnosis	28	0.38 (0.41–0.46)	59	0.37 (0.32–0.42)
Involvement of second region	58	0.39 (0.32–0.45)	225	0.40 (0.37–0.43)
Involvement of third region	71	0.45 (0.40–0.51)	285	0.63 (0.60–0.66)
Need for gastrostomy	106	0.71 (0.68–0.74)	101	0.81 (0.77–0.84)
Need for non-invasive ventilation	32	0.81 (0.77–0.86)	102	0.73 (0.69–0.78)

95% CIs are shown in brackets. Time to involvement of the third region is significantly different between those with bulbar and those with limb onset ALS. The need for gastrostomy in bulbar onset patients occurs at the equivalent time to the need for respiratory support in limb onset patients, and vice versa.

Table 3 Kaplan–Meier analysis of survival from each milestone

Last recorded milestone	Bulbar onset ALS		Limb onset ALS	
	Median (months)	5 year (%)	Median (months)	5 year (%)
Diagnosis	19	20.5	59	49.9
Involvement of second region	19	17.5	28	29.0
Involvement of third region	13	9.8	13	12.3
Need for gastrostomy	9	6.4	6	4.2
Need for non-invasive ventilation	3	5.9	8	6.0

The non-standardized median survival and 5-year survival is given from each milestone for bulbar onset and limb onset ALS in the entire cohort. The observed values provide supportive evidence of construct validity.

non-invasive ventilation for patients with limb onset ALS (Table 2). Furthermore, in patients, diagnosis tended to occur at the same time as a second region became weak, but involvement of a third region occurred earlier for patients with bulbar onset (0.45 for bulbar onset and 0.63 for limb onset, respectively; $P = 1.1 \times 10^{-7}$).

The use of riluzole also influenced timings. In limb onset ALS, the standardized time to diagnosis in patients on riluzole (0.29) was significantly earlier than in patients not on riluzole (0.39; $P = 0.035$ by Mann–Whitney test). This was not observed for those with bulbar onset ALS, but the sample size was smaller and therefore had less power. There was no effect on other milestones.

Validity of the system for staging

There is considerable evidence that the system is validated for staging. Construct validity is the extent to which a system measures what it is supposed to measure (Smith, 2005). For the milestones to be useful for staging, they should correspond correctly to survival times from the milestone to death or censor date in the entire cohort, not just those who have died. We therefore performed Kaplan–Meier survival analysis (Table 3 and Fig. 2). In the ALS cohort overall, the result clearly shows the groups can be distinguished and this is also apparent for the limb onset ALS and bulbar onset subgroups, consistent with the system having construct validity.

Furthermore, we examined 5-year survival from each milestone. If the system has construct validity, earlier stages should show bias towards individuals with a propensity for longer survival, and later stages should be biased towards those with shorter survival, which is what we observed (Table 3).

Finally, the fact that using every available milestone or just the last recorded milestone makes very little difference to the results is evidence of concurrent validity (Table 1).

Discussion

We have shown that simple clinical milestones tend to occur at predictable times within the natural disease progression of ALS. Weakness in a second region, weakness in a third region and the need for gastrostomy or respiratory support occur at distinct times, corresponding to ~40, 60 and 80% of the disease course, respectively, with diagnosis tending to occur, in our centre, at ~35% of the way through. Gastrostomy is on average needed before respiratory support for patients with bulbar onset, but the opposite is true for patients with limb onset. We therefore propose the following simple staging system for ALS:

Stage 1: Symptom onset (involvement of first region).
Stage 2A: Diagnosis.
Stage 2B: Involvement of a second region.
Stage 3: Involvement of a third region.
Stage 4A: Need for gastrostomy.
Stage 4B: Need for respiratory support (non-invasive ventilation).

The highest stage is taken if needed. For example, someone presenting with profound respiratory failure requiring non-invasive ventilation would have Stage 4B ALS, not Stage 2A.

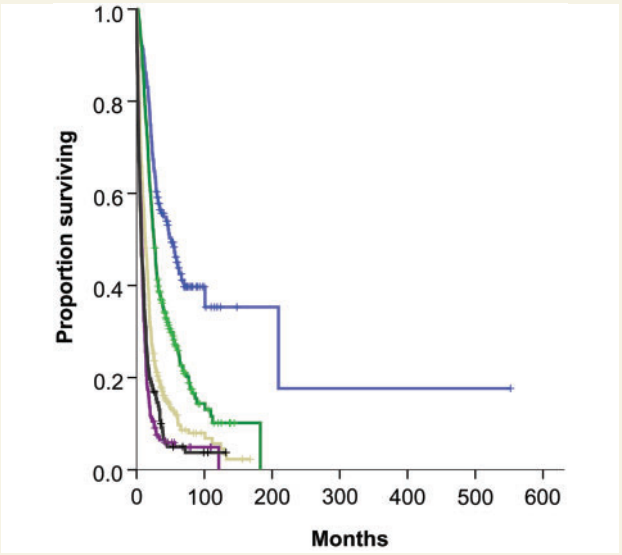

Figure 2 Kaplan–Meier curve showing survival for entire cohort from last recorded milestone to death or censor date. The separation of the curves is evidence of construct validity. Blue = diagnosis; green = second region involved; grey = third region involved; black = gastrostomy needed; purple = respiratory support needed.

The advantage of having two alternatives for Stage 2 is that time to diagnosis may well differ in other health systems or clinics, whereas standardized time to second region is likely to be similar across all centres. The naming of the Stage 4 milestones is potentially problematic. Overall, there is no difference between the standardized time to gastrostomy and respiratory support (Table 1) but this hides the fact that the order in which they occur differs between those with bulbar and those with limb onset (Table 2). Numbering them as Stages 4 and 5 would not therefore lead to a consistent system, and in addition, it is very unusual for staging systems in other diseases to have a Stage 5. We therefore propose using Stage 4 for both but with a suffix to allow separation and recognition that the events are separate milestones.

This staging system is easy to use because it corresponds both to information relevant to the neurologist and symptoms reported by the patient. It differs from the El Escorial classification (Brooks, 1994; World Federation of Neurology, 1995) because there is no requirement for upper and lower motor neuron involvement, simply evidence of neurological weakness. For example, someone with a brisk jaw jerk and dysarthria, wasting of the small hand muscles, lower limb spasticity and brisk limb reflexes would have El Escorial 'possible ALS' on the basis of only one functional region showing both upper and lower motor neuron involvement, but would have Stage 3 ALS on the basis of involvement of three functional regions. Similarly, someone with an isolated but severe respiratory onset at presentation is at Stage 4B, despite having El Escorial 'possible ALS' at best. It is well recognized that a patient might require non-invasive ventilation or even die with a 'possible ALS' diagnosis (Ince *et al.*, 1998), whereas it would be impossible for this situation to arise without the patient having reached Stage 4B.

Progression through the disease stages at predictable times is consistent with previous observations that disease progression is curvilinear (Gordon *et al.*, 2010), and that prognosis is predictable from the rate of early symptom progression or diagnostic delay (Chio *et al.*, 2002; Turner *et al.*, 2002). While we recognize that, for example, time to gastrostomy is not the same as nutritional decline, it is a milestone reached after other nutritional interventions such as changes to dietary consistency and the use of fortified supplements have been tried and is therefore likely to occur at about the same disease stage. A study using a similar methodology of examining events as a function of proportion of disease elapsed, found that medical equipment needs also occur at predictable time points (Bromberg *et al.*, 2010).

A weakness of this study is that we have used a prevalent cohort rather than an incident cohort to develop the milestones. Prevalent cohorts differ in many ways from incident cohorts. For example, they tend to be younger, live longer, have a higher proportion of male patients and fewer with bulbar onset (Huisman *et al.*, 2011). We have used standardized timings as a proportion between onset and death to generate the staging system, but it is possible that such timings differ between cohorts of different ages, sex proportions and phenotypes. The order of the milestones is very unlikely to differ, since one cannot have three regions affected before two regions, and interventions such as non-invasive ventilation or gastrostomy tend to occur towards the end of life, but the study should be repeated in an incident cohort to explore cohort effects, if any, on the standardized timings.

A further weakness is that we have not included a measure of cognitive impairment. Cognitive impairment in ALS does not occur as a fixed event that can act as a milestone as it can happen at any point in the disease course, and may vary from no impairment to frank dementia. Thus, although cognitive impairment is an important prognostic, diagnostic and functional factor, it cannot be easily integrated into a staging system because it does not fulfil one of the three requirements, that of occurring at a predictable time. The staging system is flexible enough to accommodate this in the future if needed however, for example by the addition of a suffix such as 'CI' to the stage to denote cognitive impairment.

A validated ALS staging system has several benefits. Each stage requires different types of professional and institutional resources (Radunovic *et al.*, 2007; Zoccolella *et al.*, 2007; Pinto *et al.*, 2009), with Stage 1 requiring access to health care diagnostic services, Stages 2 and 3 increasing use of the multidisciplinary team, and Stage 4 requiring intervention, end of life palliation and care. Staging can therefore be used to easily assess resource provision in relation to need.

Clinical stage can also be used as a secondary endpoint for clinical trials. Using a functional secondary endpoint such as the ALS Functional Rating Scale may result in bias because it can only be measured in those remaining alive who by necessity have a better score, and it will therefore tend to be the same in each treatment group regardless of the effect of therapy. Statistical methods exist to work around this problem (Henderson *et al.*, 2000), but using standardized time to a particular stage would not suffer from this bias and might allow assessment of what stage treatment exerts it maximal effect. For example, in this study, time to Stage 2A in patients with limb onset was reached

at 0.29 through the disease course for those on riluzole, compared with 0.39 for those not taking riluzole. There are three possible interpretations of this. It might be a false positive (we have performed four independent and four dependent tests and so there is a multiple testing burden), but the alternatives are that those who subsequently take riluzole are seen more quickly perhaps because they are more motivated, or that the overall survival is increased following diagnosis and treatment (Bensimon *et al.*, 1994), so the proportion of time at which diagnosis occurs comes earlier. We can test this by looking at the actual time to diagnosis in each group. If the standardized time is reduced in one group but the actual times are equal, this suggests the denominator is larger (overall disease length is longer) in those with the smaller standardized time to diagnosis. We find the actual time is also shorter suggesting that we are not observing a survival effect of riluzole but a bias.

Validation of this staging system will require further studies in other populations, in population registers and in other clinic databases. The standardized times to milestones may vary between different studies and populations, although the stages themselves and their meanings are likely to remain unchanged.

In conclusion, we propose a partially validated staging system for ALS based on simple clinical milestones of the natural history of ALS where each stage reflects the severity of the disease. We recommend validation in a larger population-based prospective cohort. This system may be of use for clinical practice, resource allocation and clinical trials.

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