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Investigating Geographical Differences in Time from ALS Symptom Onset to Key Disease Milestones: Data from a Real-World Survey

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INTRODUCTION

- Amyotrophic lateral sclerosis (ALS) is a heterogeneous progressive neurodegenerative disease with a mean survival of 36 months from symptom onset.[1,2]
- Clinical milestones reflect disease progression and functional loss in people living with ALS and occur at specific points in the disease course; with each milestone, medical costs increase substantially.[3,4]
  - Information on the time to reach key disease milestones may help people with ALS, caregivers, physicians, and healthcare providers to plan for optimal care.
  - A previous study suggested there may be differences in time from symptom onset to disease milestones between people in the USA and those in Europe[5]; however, geographical differences and their impact on disease milestones are not fully understood in a real-world setting.

OBJECTIVE

- To estimate and compare the time from symptom onset to key disease milestones for people with ALS in the USA, UK, Germany, France, Italy, and Spain.

METHODS

- Data were drawn from the Adelphi ALS Disease Specific Programme™ (DSP), a multinational, cross-sectional survey of neurologists and people with ALS under their care in the USA, UK, Germany, France, Italy, and Spain.
  - Data were collected between July 2020 and March 2021. The DSP methodology details were previously published.[6]
  - Briefly, neurologists completed questionnaires regarding demographics, disease milestones, and clinical outcomes, including ALS Functional Rating Scale-Revised (ALSFRS-R) scores and symptom duration, for people with ALS under their care.
- Disease milestones were defined as key events occurring during the disease course, encompassing aspects of disease progression and functional loss in ALS.
  - For each country, we evaluated the mean time from symptom onset in months to the following milestones: first consultation for ALS-related symptoms, ALS diagnosis, employment change, and need for a walking aid, caregiver support, wheelchair, communication aid, respiratory aid, gastrostomy, eye-gaze technology, and care facility.
  - Each analysis included only patients reaching the respective milestone.
- Disease progression rate was calculated (= *48 – ALSFRS-R score / symptom duration in months*) for each person with ALS and the mean presented for each country. Based on this dataset, disease progression rate (in points/month) was divided into tertiles of slow (≤0.36), intermediate (>0.36 to <0.77), and fast (≥0.77).
- Patient characteristics and time to key milestones were compared across the 6 countries using ANOVA, chi-square, or Fisher's exact test (P<0.05 considered significant).

RESULTS

- This analysis included 867 people with ALS (mean age 61.3 years; 63% were male).
- On average, people with ALS in the USA were younger and had a shorter time since symptom onset compared with those in Europe (**Table 1**). Approximately one-third of people with ALS in the USA were on riluzole alone compared with over two-thirds in the UK, Germany, France, Italy, and Spain.
- The time from symptom onset to most disease milestones was, on average, shortest in the USA and longest for those in Italy (**Figure 1, Table 2**).
  - The differences across countries were statistically significant for all milestones except care facility, which may be due to the small sample size (**Table 2**).
- For the USA, UK, Germany, France, Italy, and Spain, respectively:
  - Mean (95% CI) time from symptom onset to ALS diagnosis was 5.7 (4.9–6.5), 8.0 (6.7–9.2), 8.2 (6.3–10.2), 8.3 (6.9–9.6), 10.4 (8.5–12.4), and 11.0 (7.6–14.5) months (P<0.0001) (**Table 2**).
  - Mean disease progression rate was 0.83, 0.74, 0.71, 0.72, 0.63, and 0.60 ALSFRS-R points/month (P=0.009) (**Table 3**).
  - The proportions of slow, intermediate, and fast progressors were significantly different between countries: the USA had the highest proportion of fast progressors, and Spain had the highest proportion of slow progressors (**Table 3**).

Table 1. Demographic and clinical characteristics

Characteristic	USA (n=340)	UK (n=76)	Germany (n=65)	France (n=114)	Italy (n=119)	Spain (n=153)	All patients (N=867)	*P* value[a]
Age, mean (SD), years	59.9 (10.4)	63.0 (10.6)	60.0 (9.7)	65.6 (10.0)	62.1 (11.7)	60.4 (12.8)	61.3 (11.1)	<0.0001
Male, n (%)	223 (65.6)	52 (68.4)	40 (61.5)	70 (61.4)	65 (54.6)	92 (60.1)	542 (62.5)	0.2944
White, n (%)	279 (82.1)	70 (92.1)	63 (98.4)	110 (96.5)	113 (95.0)	137 (89.5)	772 (89.1)	<0.0001
BMI, mean (SD), kg/m^2	24.7 (5.4)	24.2 (3.2)	24.7 (2.6)	23.5 (3.3)	23.8 (2.8)	24.3 (3.5)	24.3 (4.2)	0.1508
ALSFRS-R total score, mean (SD)	33.6 (12.5)	33.9 (10.8)	31.6 (10.7)	35.2 (9.9)	31.7 (13.5)	33.4 (12.6)	33.4 (12.1)	0.2824
Time since diagnosis, mean (SD), mo	16.4 (18.3)	14.9 (13.9)	18.2 (11.3)	17.1 (16.8)	27.0 (35.3)	23.4 (27.5)	19.2 (22.7)	<0.0001
Time since symptom onset, mean (SD), mo	22.3 (21.7)	23.2 (14.4)	26.5 (14.3)	25.5 (19.8)	37.5 (37.6)	34.5 (38.0)	27.4 (27.4)	<0.0001
ALS site of onset: bulbar, n (%)	59 (17.4)	17 (22.4)	25 (38.5)	22 (19.3)	20 (17.2)	26 (17.1)	169 (19.6)	0.0043
ALS therapies, n (%)								
Riluzole alone	115 (33.8)	58 (76.3)	57 (87.7)	97 (85.1)	92 (77.3)	122 (79.7)	541 (62.4)	
Edaravone alone	93 (27.4)	–	–	–	–	–	93 (10.7)	<0.0001
Riluzole plus edaravone	61 (17.9)	–	–	–	–	–	61 (7.0)	
No ALS-approved treatment	71 (20.9)	18 (23.7)	8 (12.3)	17 (14.9)	27 (22.7)	31 (20.3)	172 (19.8)	

– Data not collected. Data on edaravone use in the UK, Germany, France, Italy, and Spain were not collected because edaravone is not approved in these countries for this indication.
[a] Comparing all countries.
BMI, body mass index.

Table 2. Time from symptom onset to key disease milestones by country

	USA (n=340)		UK (n=76)		Germany (n=65)		France (n=114)		Italy (n=119)		Spain (n=153)		All patients (N=867)		*P* value[a]
	n	Mean (95% CI), mo	n	Mean (95% CI), mo	n	Mean (95% CI), mo	n	Mean (95% CI), mo	n	Mean (95% CI), mo	n	Mean (95% CI), mo	n	Mean (95% CI), mo	
First consultation	311	3.2 (2.5–3.9)	67	2.8 (2.0–3.5)	60	4.3 (2.9–5.6)	107	4.4 (3.4–5.4)	113	4.5 (3.8–5.2)	149	4.6 (3.7–5.5)	807	3.9 (3.5–4.2)	0.0165
Diagnosis	329	5.7 (4.9–6.5)	73	8.0 (6.7–9.2)	65	8.2 (6.3–10.2)	112	8.3 (6.9–9.6)	119	10.4 (8.5–12.4)	152	11.0 (7.6–14.5)	850	8.0 (7.3–8.8)	<0.0001
Employment change	103	12.2 (9.1–15.4)	18	14.1 (9.1–19.1)	24	15.4 (10.8–19.9)	15	13.5 (9.0–18.0)	23	38.6 (17.9–59.2)	64	16.1 (12.2–19.9)	247	16.2 (13.6–18.8)	<0.0001
Walking aid	167	14.6 (12.2–17.0)	28	14.7 (10.9–18.5)	23	20.8 (14.9–26.7)	51	15.9 (13.0–18.8)	39	25.3 (16.3–34.2)	60	21.8 (17.3–26.3)	368	17.5 (15.8–19.2)	0.0017
Caregiver support	224	13.9 (12.0–15.9)	48	14.1 (11.4–16.8)	49	23.8 (20.5–27.1)	78	14.8 (12.4–17.3)	69	29.5 (20.8–38.1)	107	22.9 (17.1–28.8)	575	18.5 (16.7–20.3)	<0.0001
Wheelchair	71	18.7 (15.1–22.4)	21	16.9 (11.4–22.4)	15	26.9 (21.7–32.0)	22	22.3 (16.2–28.5)	27	35.8 (19.4–52.2)	39	23.1 (18.8–27.3)	195	22.8 (19.9–25.7)	0.0062
Communication aid	75	19.6 (15.3–24.0)	12	22.7 (13.0–32.3)	12	28.6 (23.4–33.8)	12	16.0 (8.7–23.2)	14	42.2 (9.1–75.3)	33	30.9 (23.6–38.2)	158	24.6 (20.7–28.5)	0.0128
Respiratory aid	117	21.6 (17.6–25.5)	15	22.0 (15.6–28.4)	21	31.1 (25.5–36.6)	33	24.1 (18.3–30.0)	36	41.0 (25.6–56.4)	39	34.5 (28.4–40.6)	261	27.3 (24.2–30.4)	0.0006
Gastrostomy	78	22.3 (17.5–27.1)	13	21.7 (17.1–26.2)	12	30.1 (26.8–33.5)	13	31.3 (18.2–44.3)	26	47.9 (26.7–69.1)	27	29.9 (22.7–37.1)	169	28.6 (24.4–32.9)	0.0033
Eye technology	38	17.8 (12.0–23.5)	0	NA (NA–NA)	1	26.7 (NA–NA)	2	40.9 (–21.0, 102.8)	7	73.0 (6.8–139.3)	13	39.6 (29.0–50.3)	61	29.7 (21.2–38.2)	0.0004
Care facility	27	27.7 (17.4–37.9)	5	7.5 (0.3–14.7)	5	32.4 (16.8–48.0)	7	24.5 (11.0–37.9)	8	61.2 (5.0–117.5)	8	26.2 (11.0–41.3)	60	30.3 (21.8–38.8)	0.069

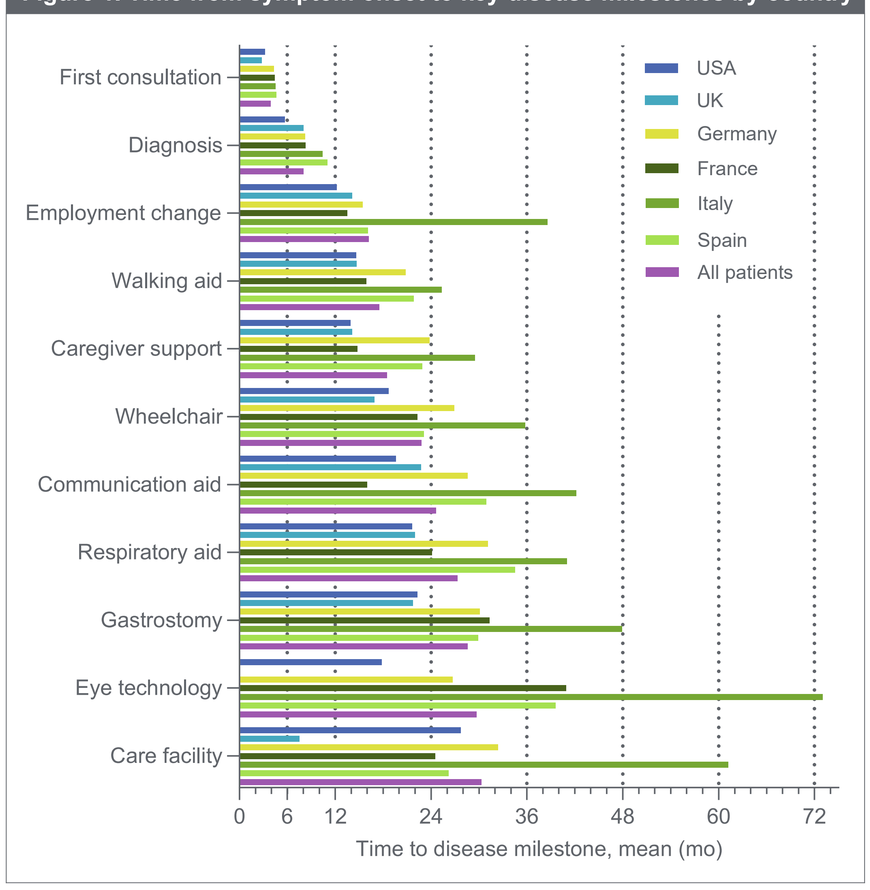
[a] Comparing all countries.
NA, not applicable.

Table 3. Rate of disease progression by country

	USA (n=340)	UK (n=76)	Germany (n=65)	France (n=114)	Italy (n=119)	Spain (n=153)	*P* value[a]
Disease progression rate,[b] mean (SD)	0.83 (0.74)	0.74 (0.68)	0.71 (0.56)	0.72 (0.60)	0.63 (0.54)	0.60 (0.70)	0.009
Slow progressors, n (%)	101 (29.7)	26 (34.2)	15 (23.1)	36 (31.6)	41 (34.5)	66 (43.1)	
Intermediate progressors, n (%)	97 (28.5)	23 (30.3)	31 (47.7)	44 (38.6)	41 (34.5)	51 (33.3)	0.005
Fast progressors, n (%)	142 (41.8)	27 (35.5)	19 (29.2)	34 (29.8)	37 (31.1)	36 (23.5)	

[a] Comparing all countries.
[b] ALSFRS-R score lost per month.

Figure 1. Time from symptom onset to key disease milestones by country



Limitations

- Data from the survey are cross-sectional, with limited information about individual patient journeys or disease history.
- Participation was affected by the willingness to complete the survey and may not reflect a random sample of neurologists or people with ALS.

CONCLUSIONS

- This analysis of real-world data showed that, irrespective of country of residence, people with ALS quickly reached various disease milestones, demonstrating rapid disease progression.
- Variation in time to reach specific milestones was observed across countries, with the time from symptom onset to key disease milestones tending to be shortest for people with ALS in the USA and longest for those in Italy.
- This variation may in part reflect differences in the healthcare systems of the participating countries, in addition to variation in rate of disease progression observed in this study among people with ALS from different countries.

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Disclosures

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Abbreviations

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; ANOVA, analysis of variance; DSP, Disease Specific Programme.

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