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Original Article

Characteristics and factors associated with independence in the activities of daily living of patients with amyotrophic lateral sclerosis at diagnosis

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Abstract. [Purpose] To investigate the characteristics and factors associated with independence in the activities of daily living in patients with amyotrophic lateral sclerosis at diagnosis based on clinical phenotypes. [Participants and Methods] Fifty-seven participants diagnosed with amyotrophic lateral sclerosis were assessed using the Barthel Index. Participants were classified into three clinical phenotypes (bulbar-onset, upper limb-onset, and lower limb-onset), and the total and subitem scores were compared. To statistically examine factors associated with independence in the activities of daily living, the participants were divided into two groups: Barthel Index of 100 and ≤95. [Results] The total, bulbar-onset, upper limb-onset, and lower limb-onset Barthel Index scores were 87.9 ± 17.7, 96.7 ± 5.9, 92.5 ± 11.9, and 70.0 ± 22.2, respectively. The Total Barthel Index and lower limb-related activities of daily living scores were significantly lower in the lower limb-onset group, and knee extension muscle strength was identified as a factor associated with independence, with a cutoff value of 32.0%. [Conclusion] Patients with lower limb onset had more impairments in lower limb-related activities of daily living than those with other clinical phenotypes. To maintain independence in patients with amyotrophic lateral sclerosis at diagnosis, it is necessary to improve knee extension muscle strength through exercise and perform environment adjustments using the cutoff values as indicators.

Key words: Amyotrophic lateral sclerosis, Activities of daily living, Phenotype

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive disease that occurs in middle or later age and causes degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord. It generally begins with muscle weakness in the limbs and progresses gradually throughout the body. However, in one-third of patients, bulbar symptoms precede the onset of ALS[1, 2)]. Muscle weakness, spasticity, respiratory failure, and communication difficulties limit the activities of daily living (ADL) and social participation of patients. The time from onset to death or the need for invasive ventilation is 20–48 months[3)]. Riluzole and edaravone have been approved for the treatment of ALS in Japan. However, riluzole only prolongs survival for 2–3 months but does not improve motor function[4)], and the effect of edaravone in inhibiting disease progression is limited to patients with mild disease[5)]. Exercises are performed, and assistive devices and social services have been introduced to maintain and improve the ADL of patients[6)].

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The clinical phenotype of ALS is divided into bulbar-onset, upper limb-onset, and lower limb-onset, and the early stages of the disease show a variety of disabilities depending on the phenotype[7, 8]. Therefore, it is necessary to consider exercise and welfare equipment according to disability from the time of diagnosis; however, there are no reports on the ADL disability of patients with ALS according to stage or clinical phenotype. We investigated the characteristics of ADL based on clinical phenotype and the factors associated with ADL independence in patients with ALS at diagnosis.

PARTICIPANTS AND METHODS

This study was approved by the Ethics Committee of the Osaka University Hospital (approval number: 22548). Informed consent was opted out in accordance with the rules of the Ethics Committee. Personal information was anonymized and no personally identifiable information was included. A summary of the study is available online at https://www.hosp.med.osaka-u.ac.jp/research/data/rehabilitation7.pdf.

The participants were admitted to Osaka University Hospital between April 2015 and June 2023, diagnosed with ALS, and prescribed rehabilitation. The diagnoses were made by a neurologist based on the Awaji criteria[9]. Of the 64 patients included, one was excluded because of psychiatric disorders affecting ADL and six were excluded because of missing data (Fig. 1).

The survey items included age, sex, body mass index (BMI), time since onset, Barthel Index (BI)[10], ALS functional rating scale-revised (ALSFRS-R)[11], Geriatric Nutritional Risk Index (GNRI)[12], % forced vital capacity (FVC), grip strength, knee extension muscle strength, and the presence of spastic gait. The GNRI was based on albumin levels, and the %FVC was based on the results of respiratory function tests at admission. Grip strength was measured using the Grip-D (Takei Kiki Kogyo, Inc., Niigata, Japan) once on each side under maximum effort in the sitting position, according to a previous study[13]. Knee extension muscle strength was measured three times under maximum effort in the sitting position and in 90° flexion at the hip and knee joints using the μ-Tas (Anima, Inc., Tokyo, Japan), according to a previous study[14]. The average of three measurements was divided by body weight to obtain the percentage. Grip and knee extension muscle strengths were calculated as the mean of the left and right sides. Spastic gait was evaluated in patients who could walk independently or with assistance.

Based on a previous study[8], the participants were classified into three clinical phenotypes (bulbar-onset, upper limb-onset, and lower limb-onset), and their clinical information was compared. Continuous variables were examined using the Kruskal–Wallis test, and categorical variables were examined using Fisher's exact test. Holm's multiple comparisons were added as a subtest for items that showed significant differences.

The patients were also divided into two groups: patients with a BI score of 100 and patients with a BI score of ≤95. A single regression analysis was conducted using these two groups as the objective variables, and each variable of clinical information were used as an explanatory variable. Logistic regression analysis using the method of variable reduction was conducted using clinical information with p-values <0.1 in the single regression analysis as the explanatory variable. Multicollinearity between the variables was assessed using the variance inflation factor. The extracted variables were subjected to receiver operating characteristic curve analysis to calculate the cutoff values. The analyses were performed using the statistical software EZR version 1.67[15]. Statistical significance was set at $p<0.05$.

RESULTS

The participants' clinical information is presented in Table 1. Age, sex, BMI, time since disease onset, ALSFRS-R, GNRI, grip strength, and spastic gait did not differ significantly between the clinical phenotypes. There were significant differences

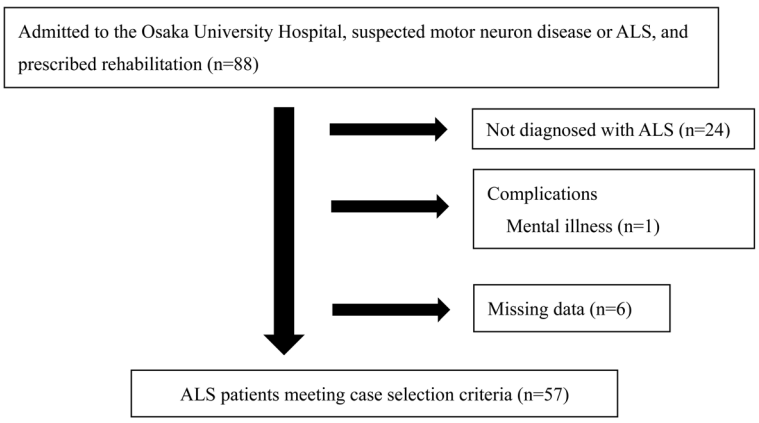

Fig. 1. Case selection process.
ALS: amyotrophic lateral sclerosis.

Table 1. Clinical information of the participants

	Whole (n=57)	B (n=18)	UL (n=24)	LL (n=15)	Comparison between the three groups	Lower tester		
						B-UL	B-LL	UL-LL
Age (years)	65.9 ± 11.1	68.9 ± 9.9	63.0 ± 11.4	66.9 ± 11.8				
Sex (M:F)	38:19	10:8	16:8	12:3				
BMI (kg/m^2)	21.4 ± 3.2	20.8 ± 2.7	21.7 ± 3.7	21.5 ± 3.0				
Period after onset (months)	17.7 ± 11.9	15.2 ± 8.0	20.6 ± 14.9	16.1 ± 10.0				
ALSFRS-R	39.5 ± 5.1	39.3 ± 4.3	41.1 ± 4.7	37.1 ± 5.7				
GNRI	106.2 ± 8.4	104.8 ± 9.8	106.5 ± 8.0	106.9 ± 7.3				
%FVC (%)	75.8 ± 22.5	62.9 ± 21.9	81.6 ± 20.7	81.8 ± 20.6	*	*	*	
Grip strength (kg)	18.1 ± 10.4	18.2 ± 10.0	14.9 ± 8.2	23.1 ± 12.5				
Knee extension muscle strength (%)	34.6 ± 16.2	39.4 ± 15.4	39.4 ± 13.5	21.2 ± 14.1	**		**	**
Spastic gait (Y: N), n=51	10: 41	2: 16	4: 19	4: 6				

*p<0.05, **p<0.01.
ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; B: bulbar-onset; BMI: body mass index; F: female; FVC: forced vital capacity; GNRI: Geriatric Nutritional Risk Index; LL: lower limb-onset; M: male; UL: upper limb-onset; Y: yes; N: no.

in %FVC (p=0.01) and knee extension muscle strength (p<0.01); %FVC was lower in patients with bulbar-onset (bulbar-upper limb p=0.02, bulbar-lower limb p=0.045) and knee extension was muscle strength in patients with lower limb-onset (bulbar-lower limb p<0.01, upper limb-lower limb p<0.01).

The BI by clinical phenotype is shown in Table 2. The total BI scores were 87.9 ± 17.7 (mean ± standard deviation), and 96.7 ± 5.9, 92.5 ± 11.9, and 70.0 ± 22.2 for bulbar, upper limb, and lower limb-onsets, respectively. For the clinical phenotypes, the percentages of participants with BI scores of 100 were 72%, 58%, and 13%, respectively. The BI scores were significantly lower in patients with lower limb-onset than in those with bulbar- or upper limb-onset (p<0.01 for three groups, bulbar-lower limb and upper limb-lower limb).

The percentage of patients who required monitoring or assistance based on the BI sub-items was 22% for bathing and stair climbing in the bulbar-onset group; 33% for dressing, 29% for bathing, and 21% for stair climbing in the upper limb-onset group; and 87% for stair climbing, 80% for bathing and walking, 60% for dressing, 47% for toileting, and 33% for transferring in the lower limb-onset group. In terms of lower limb onset, walking and stair climbing were most frequently performed with total assistance, with 54% and 33% of patients receiving total assistance for stair climbing and walking, respectively. The scores for transferring, bathing, walking, and stair climbing were significantly lower for lower limb-onset than for bulbar and upper limb-onsets (for all items, p<0.01 for the three groups, bulbar-lower limb and upper limb-lower limb), and the scores for bathing and dressing were significantly lower for the lower limb-onset group than for the bulbar-onset group (p<0.01 for three groups and bulbar-lower limb) (Table 2).

The single regression analysis identified the %FVC (p=0.09) and knee extension muscle strength (p<0.01) as factors associated with ADL independence (Table 3). Further logistic regression analysis confirmed that knee extension muscle strength was related to independence in ADL (p<0.01, odds ratio: 1.12, 95% confidence interval: 1.05–1.19). The cut-off value for knee extension muscle strength was 32.0% (sensitivity: 75.0%, specificity: 86.2%).

DISCUSSION

The demographic information and disease severity of patients did not differ significantly between the clinical phenotypes. The %FVC and knee extension muscle strength decreased at the primary site; however, grip strength and GNRI scores were not significantly different. The lower limb muscle strength decreased owing to inactivity when walking and stair climbing are impaired or when there is a fear of falling[16]. In contrast, upper limb muscle strength is considered less susceptible to disuse muscle atrophy due to inactivity compared to lower limb muscle strength[17]. Therefore, it was considered that the decrease in grip strength was not significant in the upper limb-onset group. In terms of GNRI, which indicates nutritional status, a score of less than 92 was considered to be moderate or high nutritional risk, while 99% of mild cases (ALSFRS-R ≥37 points) are reported to be at no nutritional risk or at low risk[18]. In the present study, the mean GNRI was 104.8 even in patients with bulbar-onset, with no significant difference between clinical phenotypes.

The BI is a representative ADL evaluation method that is adjusted to evaluate 10 performance items on a 5–15-point scale, totaling to 100 points. It is also widely used as an ADL evaluation method for ALS[19]. Standard values for ADL independence have been reported for grip strength[20], knee extension muscle strength[21, 22], nutritional status[23], and spastic gait[24], which are related to independence in walking and stairs. We hypothesize that the reason for the lack of consensus on the factors

Table 2. Barthel Index by clinical phenotype.

	Whole	B	UL	LL	Comparison between	Lower tester		
	(n=57)	(n=18)	(n=24)	(n=15)	the three groups	B-UL	B-LL	UL-LL
Total points	87.9 ± 17.0	96.7 ± 5.9	92.5 ± 11.9	70.0 ± 22.2	**		**	**
ADL Independence	51	72	58	13				
Percentage of cases (%)								
Subitem		Percentage of applicable persons (%)						
Eating	10 points	100	96	87				
	5 points	0	4	13				
	0 points	0	0	0				
Transferring	15 points	100	100	67	**		**	**
	10 points	0	0	20				
	5 points	0	0	0				
	0 points	0	0	13				
Grooming	5 points	100	83	87				
	0 points	0	17	13				
Toileting	10 points	100	88	53	**		**	
	5 points	0	13	40				
	0 points	0	0	7				
Bathing	5 points	78	71	20	**		**	**
	0 points	22	29	80				
Walking	15 points	89	92	20	**		**	**
	10 points	11	4	40				
	5 points	0	0	7				
	0 points	0	4	33				
Stair climbing	10 points	78	79	13	**		**	**
	5 points	22	13	33				
	0 points	0	8	54				
Dressing	10 points	94	67	40	**		**	
	5 points	6	25	53				
	0 points	0	8	7				
Bladder	10 points	100	100	100				
	5 points	0	0	0				
	0 points	0	0	0				
Bowel	10 points	100	100	93				
	5 points	0	0	7				
	0 points	0	0	0				

*p<0.05, **p<0.01. ADL: activities of daily living; B: bulbar-onset; LL: lower limb-onset; UL: upper limb-onset.

Table 3. Factors associated with ADL independence (single regression analysis)

	p-value	Odds ratio	95% Confidence interval
Age		0.98	0.93–1.03
Sex		1.53	0.50–4.64
BMI		1.03	0.88–1.21
Post-onset period		0.99	0.94–1.03
GNRI		1.01	0.95–1.08
%FVC	†	1.02	0.997–1.05
Grip strength		1.03	0.98–1.09
Knee extension muscle strength	**	1.12	1.05–1.19
Spastic gait		1.41	0.35–5.65

†p<0.1, *p<0.05, **p<0.01. ADL: activities of daily living; BMI: body mass index; FVC: forced vital capacity; GNRI: Geriatric Nutritional Risk Index.

associated with ADL is that no study has examined the factors associated with ADL impairment according to clinical phenotype. However, such studies have not yet been reported, and this is the first report of such a study.

In the lower limb-onset group, the total BI score was significantly lower than that of other clinical phenotypes, and the scores of the lower limb-related ADL, such as transferring, toileting, bathing, walking, and stair climbing, were lower than those of other clinical phenotypes[25]. Knee extension muscle strength was also significantly lower than other clinical phenotypes and was below the independence threshold (22% knee extension muscle strength)[22] for transferring, which is the least difficult of the lower-limb related ADL, indicating that lower limb-related ADL were impaired in general. The patients also had a low dressing score, which is an upper limb-related ADL[25]. Because knee extension muscle strength is also involved in the ability to change lower garments[26], it is thought that lower limb muscle weakness can affect the level of independence in the ADL.

Assistance for walking and stair climbing was mostly total assistance, whereas assistance for transferring, toileting, and dressing was mostly monitoring or partial assistance. Because the introduction of assistive devices for patients with ALS is effective in maintaining and improving ADL[27], the installation of a handrail or a raised chair can be used to reduce the amount of assistance and care required for transferring, toileting, and dressing.

The degree of independence in ADL varies from the time of diagnosis, and it is necessary to consider whether the patient can be monitored or partially assisted using a walker, lower limb orthosis, or handrails, and to assess whether a wheelchair or home modification is necessary for full assistance. After diagnosis, patients can use the social welfare system; therefore, it is necessary to advise and suggest the use of welfare equipment and home modification.

More than half of the patients with bulbar-onset and upper limb-onset (71%, bulbar-onset and 58%, upper limb-onset) were independent in the ADL. However, bathing and stair climbing were characteristic of ADL impairment in patients with bulbar-onset and upper limb-onset, and were common to patients with lower limb-onset. Knee extension muscle strength was related to independence in bathing and stair climbing, with a reported cutoff value of 23–24%[22]. Knee extension muscle strength was 39.4 ± 15.4% for bulbar-onset and 39.4 ± 13.5% for upper limb-onset, which means that approximately 15% of patients were below the self-reliance threshold, suggesting that lower limb muscle weakness may be involved in impaired bathing and stair climbing in both disease types. In the BI sub-item, difficulty in bathing and stair climbing was high regardless of the disease[28, 29]. Therefore, when ADL is impaired in bulbar- or upper limb-onset, the degree of difficulty in the ADL may be more influential than the clinical phenotype.

One of the ADL impairments specific to the upper limb-onset is dressing. Dressing is the most difficult aspect of upper limb-related ADL[28]. Although the grip strength to determine independence in dressing is not clear, the cutoff value for ADL using the upper limb has been reported to be 16 kg of grip strength[20]. The grip strength of patients with upper limb-onset was 14.9 kg, suggesting that unlike dressing in patients with lower limb-onset, the percentage of independence in patients with upper limb-onset decreased, mainly due to decreased grip strength.

Logistic regression analysis revealed that knee extension muscle strength was related to ADL independence, with a cutoff value of 32.0%. In this study, ADL was significantly decreased in the lower limb-onset group, and bathing and stair climbing were impaired owing to knee extension weakness, even in the bulbar-onset and part of the upper limb-onset groups. Previous studies have reported that knee extension muscle strength has been reported as a factor for determining whether a person can be independent ADL in various diseases[21, 22] and a similar association has been suggested in patients with ALS.

We reported that exercise significantly improved lower limb muscle strength in ambulatory patients with mild ALS[30] and that a case in which the effect of exercise on lower limb muscle strength lasted for 10 months[31]. However, the walking ability and the ability to climb stairs in these patients did not improve, and it was difficult for them to return to an independent level. To extend the period of independence in ADL from the time of diagnosis, it is necessary to focus on knee extension muscle strength and to attempt functional improvement through exercise, as well as early efforts to select welfare equipment and perform appropriate environment adjustments using the cutoff values as indicators.

Although upper motor neuron symptoms as well as lower motor neuron symptoms may appear first in the early post-onset period, upper limb spasticity was not investigated in the present study. However, upper limb spasticity has been reported to have little effect on ADL[32]. In the present study, upper limb-related ADL were generally independent of the clinical phenotype. Further studies are required to address these limitations.

In this study, we investigated the characteristics of ADL and factors associated with independence in patients with ALS at diagnosis according to the clinical phenotype. Patients with lower limb-onset ALS had more impaired ADL than those with other clinical phenotypes, especially lower limb-related ADL. In addition, bulbar- and upper limb-onset ADL impairments are characterized by impairments in bathing and stair climbing, which are common in lower limb-onset ADL impairments. It is difficult for patients with ALS to return to an independent level when they have reached the point of requiring monitoring and assistance with their ADL. To extend the period of independence from the time of diagnosis, it is necessary to focus on knee extension muscle strength, improve function by exercise, select welfare equipment, and adjust the environment appropriately, using the cutoff values in this study as indicators.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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