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Original Article

Lower limb muscle strengthening exercises in patients with early-stage amyotrophic lateral sclerosis: a case series study

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Abstract. [Purpose] We investigated whether patients with early-stage amyotrophic lateral sclerosis can improve their voluntary strength with a physical therapy program. [Participants and Methods] This retrospective case series study at a single university hospital included 13 patients with amyotrophic lateral sclerosis (amyotrophic lateral sclerosis functional rating scale-revised ≥35, modified functional ambulation categories score ≥4). Physical therapy was performed for 3 weeks. We investigated knee extension muscle strength and modified functional ambulation categories scores at the start and end of the therapy and calculated the improvement rate of knee extension muscle strength. We performed a regression analysis of the relationship between knee extension muscle strength at the start of the study and the improvement rate. [Results] The knee extension muscle strength improved significantly; however, the effect size was small (0.13). The modified functional ambulation categories scores did not improve significantly. The knee extension muscle strength at the start of the therapy was negatively correlated with the improvement rate (logarithmic transformed linear regression: adjusted R^2=0.27). [Conclusion] A short-duration exercise program improved lower limb muscle strength in patients with early-stage amyotrophic lateral sclerosis. Additionally, we found that patients with weaker lower limb muscle strength at the start of the therapy demonstrated greater improvement at the end of the therapy.

Key words: Amyotrophic lateral sclerosis, Exercise intervention, Muscle strength

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive disease that involves degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord; this disease begins with local weakness and gradually progresses to loss of strength in all muscles. With the appearance of clinical symptoms (e.g., muscle weakness, spasms, respiratory failure, and difficulties in communication), activities of daily living and social participation become restricted[1–3)]. Symptoms generally begin in the extremities; however, in one-third of patients, bulbar symptoms precede limb weakness[4)]. Life expectancy is 3 to 5 years, on average, from the symptom onset; many patients die of respiratory failure[5)]. In Japan, riluzole and edaravone have been approved as treatment for ALS. However, symptomatic treatment and rehabilitation remain important because there is no curative treatment[2, 3)].

Previous studies have demonstrated that resistance or concurrent exercises (such as resistance and endurance exercises) are effective for improving muscle strength in patients with mild ALS[6–9)]. However, other studies failed to show any im-

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provement[10, 11]. In general, there is conflicting evidence about the value of exercise in patients with ALS and who the best candidates might be. Therefore, it is necessary to determine the characteristics of patients whose muscle strength can improve with exercise and to investigate the mechanism underlying this improvement.

We previously reported that 2 to 3 weeks of physical therapy for ambulatory ALS patients significantly improved lower limb muscle strength, and that those with muscle strength below the normal range showed greater improvement[8]. In this previous study, we examined ambulatory ALS patients; however, the severity of motor weakness varied. Moreover, the disease duration ranged from 6 months to 9 years, and some patients had long post-onset periods, which meant very slow disease progression. Furthermore, it was difficult to compare the improvement rate among the patients because the duration of the intervention varied. Therefore, in order to reveal whether individuals with early-stage ALS can improve their voluntary strength with physical therapy program, we conducted a case series study with more uniform patient population and standardized intervention program.

PARTICIPANTS AND METHODS

This study was approved by the Osaka University Medical Hospital Ethics Committee (approval number: 18494). The requirement for informed consent was waived according to the ethics committee provisions. The details of our study are published on the website (https://www.hosp.med.osaka-u.ac.jp/research/data/rehabilitation6.pdf), and patients had the choice to withdraw from the study. Personal information was anonymized.

This retrospective case series study at a single site included consecutive 13 ALS patients who were admitted to the Osaka University Medical Hospital for diagnosis or for introducing edaravone, from April 2015 to December 2019. Eligibility criteria were as follows: disease onset within 2 years; ALS functional rating scale-revised (ALSFRS-R) score ≥35 points[12]; modified functional ambulation category (MFAC) score ≥4 without ankle foot orthosis[13]; no respiratory support during the daytime; no percutaneous endoscopic gastrostomy within the intervention period; and no severe cognitive impairment, respiratory failure, cardiovascular disease, or malignancy that may affect lower limb muscle strengthening exercises or gait exercise. Figure 1 shows the flow chart of patient inclusion. The eligibility criteria were set with the aim of making the study population as uniform as possible. All patients were diagnosed during hospitalization based on the Awaji criteria[14].

Physical therapy was implemented daily on weekdays for approximately 30 minutes by physical therapists. The intervention period was 3 weeks. Resistance training of the lower limb was performed for half of each session. The lower-limb exercises performed included leg-extension combined with weights and machine exercises for lower limb extension in the closed kinetic chain position. Bicycle ergometer, treadmill, and respiratory exercises (respiratory muscle exercises, chest and shoulder girdle flexibility exercises, etc.) were performed during the other half. Exercise intensity was moderate, based on the methodology used in previous reports[2], and adjusted to maintain a modified Borg Scale score of 5 (lower limbs)[15].

We measured knee extension muscle strength (KEMS) and the MFAC score at the start and end of physical therapy. Muscle strength was measured by using a hand-held dynamometer (μ-Tas F-1, ANIMA, Japan). The KEMS was measured as previously reported[8]. KEMS and improvement rate were calculated as follows

KEMS (Nm/kg) = (average of 3 attempts) (N) × lower leg length (m)/body weight (kg)

Improvement rate (%) = [(KEMS at end) – (KEMS at start)]/(KEMS at start) × 100%

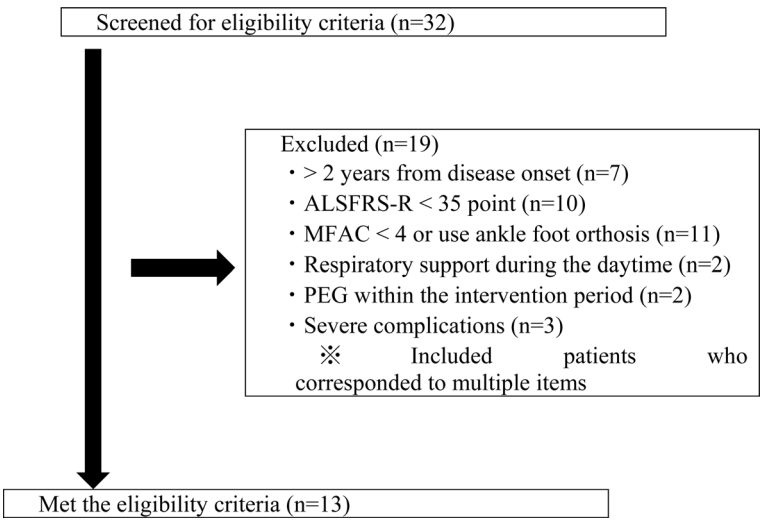

Fig. 1. Flow chart of the procedures.

We examined differences in the KEMS and MFAC score between the start and end of therapy using the Wilcoxon signed-rank test; effect sizes were also calculated using Cohen's d[16]. Cohen's d was calculated as follow:

$$d = [(\text{average of KEMS at end}) - (\text{average of KEMS at start})]/[((\text{standard deviation of KEMS at start})^2 + (\text{standard deviation of KEMS at end})^2)/2]^{1/2}$$

Next, to investigate the relationship between KEMS at the start of therapy and improvement rate, we obtained the linear functional equation and the logarithmic transformed linear regression equation. Regarding the logarithmic transformed linear regression, the KEMS was never less than zero, and the improvement rate was unlikely to be much less than zero because this study involved a short-duration intervention. We determined that this regression analysis was to be analyzed because it was more relevant to our data as the two variables may converge and plateau.

Finally, we examined the clinical characteristics related to improvement rate. We used the reported minimum clinically important difference in KEMS among patients with neurological diseases[17] to divide our patients into two groups: improvement (improvement rate ≥18% in one or both limbs) and non-improvement (improvement rate <18% or worsened in both limbs). Then, we compared clinical characteristics between the two groups using the Mann-Whitney U test and Fisher's exact test. $P<0.05$ was considered statistically significant. JMP® 14 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

RESULTS

Table 1 displays the clinical and demographic information of the patients at the start of therapy. No patient had experience with rehabilitation by physical or occupational therapists prior to admission, and none discontinued the exercise or reduced the exercise intensity during intervention. No adverse events were observed.

The KEMS improved significantly, albeit with a small effect size (0.13) (Table 2). In contrast, the MFAC scores did not improve.

Regression analysis revealed that KEMS at the start of therapy negatively correlated with the improvement rate; the adjusted coefficient of determination was 0.22 for the linear function and 0.27 for the logarithmic linear function (Fig. 2).

Regarding factors related to improvement rate, KEMS, MFAC score, and ALSFRS-R score were significantly lower in the improvement group than in the non-improvement group (Table 3).

Table 1. Demographic and clinical characteristics of ambulatory amyotrophic lateral sclerosis patients in this study

Age (years, mean ± standard deviation)	68.5 ± 5.5
Gender (male:female)	9:4
Site of onset (bulbar: upper limb: lower limb)	5:4:4
Time since disease onset (months)	11.5 ± 4.8
Riluzole (Yes:No)	13:0
Edaravone (Yes:No)	5:8
%FVC	74.4 ± 17.3
mAS of lower limbs	1 (n = 9) 1+ (n = 4)
ALSFRS-R	40.9 ± 4.1

ALSFRS-R: Amyotrophic lateral sclerosis rating scale-revised; FVC: forced vital capacity; mAS: modified Ashworth Scale.

Table 2. Course of the knee extension muscle strength-modified functional ambulation categories

	Start	3 weeks	p-value	Effect size
KEMS (Nm/kg)	1.37 ± 0.71	1.46 ± 0.69	0.004**	0.13
MFAC	5.5 ± 1.3	5.7 ± 1.2	0.15	0.16

KEMS: knee extension muscle strength; MFAC: modified functional ambulation categories.
**p<0.01.

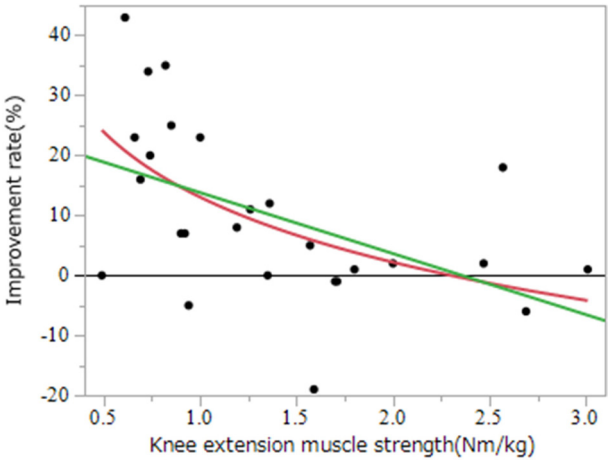

Fig. 2. Relationship between knee extension muscle strength at the start and the improvement rate.
Linear regression equation (Improvement rate)=24.0 −10.2 ×(KEMS) R^2=0.22**
Logarithmic transformed linear regression equation (Improvement rate)=13.0 −15.7 ×log (KEMS) R^2=0.27**
**p<0.01.

Table 3. Differences in the baseline clinical characteristics between the improvement and non-improvement groups

	Improvement (n=7)	Non-improvement (n=6)	p-value
Age (years)	70.1 ± 6.8	66.7 ± 3.0	0.39
Gender (male:female)	5:2	4:2	1.00
Site of onset (bulbar + upper limb: lower limb)	5:2	4:2	1.00
Edaravone (Yes:No)	2:5	3:3	0.59
Time since disease onset (months)	10.9 ± 3.3	12.3 ± 6.4	1.00
%FVC	69.9 ± 10.5	79.6 ± 23.0	0.30
KEMS (Nm/kg)	1.15 ± 0.69	1.63 ± 0.66	0.002**
Lower limb mAS scores (1:1+)	5:2	5:1	1.00
MFAC scores	4.6 ± 0.8	6.7 ± 0.5	0.008**
ALSFRS-R scores	38.3 ± 3.4	44.0 ± 2.2	0.01*

ALSFRS-R: Amyotrophic lateral sclerosis rating scale-revised; FVC: forced vital capacity; KEMS: knee extension muscle strength; mAS: modified Ashworth Scale; MFAC: modified functional ambulation categories.
*p<0.05, **p<0.01.

DISCUSSION

We implemented a 3-week physical therapy program for mild and ambulatory ALS patients. Generally, at least a few weeks are required for the diagnosis and the initiation of treatment of ALS patients. Therefore, evaluating whether a 3-week physical therapy regimen is effective in improving muscle strength and gait ability may help neurologists decide the appropriate goals and methods of treatment interventions. As a result of this study, KEMS improved significantly; however, the improvement rate was only 7% and effect size was small (0.13), which corroborated the findings of a previous study[2]. Furthermore, no significant difference was found in the MFAC score, which led to lack of improvement in gait ability. Short duration effects of moderate exercise (strength exercises or functional training) on KEMS in other neurological diseases (e.g., stroke and polymyositis/dermatomyositis) showed improvement rates of >30% and effect sizes of >0.9[18–20]. Our results indicated that the improvement rate and effect size in ALS were smaller than those in other neurological diseases and that patients with ALS had a poor response to exercise.

Next, we examined the relationship between KEMS at the start of therapy and the improvement rate. We found that KEMS at the start of therapy was negatively correlated with the improvement rate. When we compared the linear regression and the logarithmic transformed linear regression, the logarithmic transformed linear regression showed a higher adjusted coefficient of determination. It is unlikely that the muscle strength would decrease significantly in the natural course for 3 weeks. We believe that the logarithmic transformed linear regression exhibited a higher adjusted coefficient of determination

because the improvement rate became closer to the plateau as the muscle strength became higher. These findings suggest that improvement should be expected in more impaired patients with the current eligibility criteria.

We divided patients into improvement and non-improvement groups and compared the clinical characteristics of these groups. We found that the improvement group exhibited ALSFRS-R and MFAC scores that were 5.7 points and 2.1 points lower, respectively, than those of the non-improvement group. The improvement group exhibited KEMS that was 70% of that of the initial value in the non-improvement group. One of the reasons why the improvement group had lower function may be attributable to disuse in addition to the natural disease course. In ALS patients, along with muscle weakness, other symptoms, including spasms, fear of falling, balance impairment, and fatigue can worsen gait ability[21]. Notably, even ambulatory ALS patients must adapt to a more sedentary lifestyle[22]. The improvement group had a higher ALSFRS-R score than the initial score in the non-improvement group. We believe that slight progression of symptoms led to adaptation of a sedentary lifestyle, resulting in disuse muscle weakness. Regarding improvement of muscle strength by exercise, 3 weeks of intervention may be too short to observe meaningful responses to an exercise intervention; nevertheless, some studies reported that exercise for several weeks improved muscle strength with physiological changes[23, 24]. Del Vecchio et al. reported that 4-weeks of exercise generated changes in muscle strength because of neural adaptations in normal participants[23]. Itoh et al. reported that responses to muscle strengthening exercises were more rapid in atrophied muscles than in normal muscles and that the effect of muscle strengthening exercises could be achieved with only 1 week of intervention[24]. Based on these findings, we believe that the physical therapy improved disuse muscle weakness in the improvement group.

Conversely, in the non-improvement group, KEMS was 1.63 Nm/kg, which was presumed to exceed the normal value[25, 26], and muscle strengthening exercises were found to be less effective. The patients assigned to this group were found to have this outcome an average of 12 months after the onset, and it is estimated that approximately 70% of motor neurons degenerate one year after onset[27]. Therefore, disuse muscle weakness was thought to have been prevented in these patients at the start of therapy. It is unclear why this occurred; however, in addition to the greater gait ability, nutritional status and daily physical activity may have contributed to this result.

These data suggest that, in mild and ambulatory ALS patients, physical therapy significantly improved lower limb muscle strength; nevertheless, the effect size was small in this study. Focusing on the relationship between lower limb muscle strength at the start and improvement rate, lower limb muscle strength negatively correlated with the improvement rate. Muscle weakness may be exacerbated partly due to disuse in some patients, and the effect of exercises should be expected to improve disuse muscle weakness in more impaired patients with the current eligibility criteria.

This study had several limitations. First, the sample size was small; furthermore, a control group was not included. Large randomized controlled trials are needed to confirm our results. Next, in this study, all patients took riluzole and five patients took edaravone. Therefore, it cannot be denied that these medications could have improved muscle strength. Nevertheless, because a previous study showed no effect of improved muscle strength with riluzole and edaravone[28, 29], it is thought that the effect was mainly due to exercise. With regard to the intervention, we tried to standardize the contents by unifying the time and intensity of muscle strengthening exercise. However, the details of the intervention, such as the number of sets and repetitions of resistance training and the proportion of each of the different exercises, could not completely controlled in each patient. It is unclear whether a customized and long-duration intervention would lead to further improvement of KEMS and gait ability. However, a previous study showed a decline in rather than an improvement in muscle strength with the 2-month intervention[6, 10]. These findings suggest that in patients with ALS, the effect of exercise may overcome the natural course of muscle weakness but only for a limited period. In this study, the exercise intensity was adjusted to moderate intensity (the modified Borg Scale 5); although Lunetta et al. reported that higher exercise intensity adjusted to the modified Borg Scale 7 was also safe and effective[30]. Further studies are needed to identify the optimal intensity and components of rehabilitation intervention to maximize improvement in ALS patients.

Three-week physical therapy in mild and ambulatory ALS patients significantly improved lower limb muscle strength. Muscle weakness may be exacerbated partly due to disuse in some patients, and the effect of exercises should be expected to improve disuse muscle weakness in more impaired patients with the current eligibility criteria. Physical therapy should be considered early after diagnosis to maintain and improve function in ALS patients.

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None.

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