Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8030-21
Intern Med 61: 1479-1484, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

Effects of Long-term Hybrid Assistive Limb Use on Gait in Patients with Amyotrophic Lateral Sclerosis

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Abstract:

Objective To assess the long-term effects of hybrid assistive limb (HAL) treatment on gait in patients with amyotrophic lateral sclerosis (ALS).

Methods Three courses of treatment with HAL were administered to three women with ALS. Each course had a four- to five-week duration, during which the treatment was performed nine times, with a rest period of at least two months between each course. Gait ability (2-minutes-walk and 10-m-walk tests), ALS Functional Rating Scale-Revised, and respiratory function tests were performed before and after each treatment course.

Patients Patients diagnosed with ALS, according to the updated Awaji criteria, by board-certified neurologists in the Department of Neurology and Department of Rehabilitation Medicine, Toho University Omori Faculty of Medicine between January and December 2019 were recruited.

Results The average time from the start to the end of the 3 courses was 319.7±33.7 days. A multiple regression analysis was performed for the 2-minutes-walk and 10-m-walk tests, using the baseline value, each participant's ID, and time point as covariates. Changes after each course were considered outcomes. Following the 3 treatment courses, the 2-minutes walk distance improved by 16.61 m (95% confidence interval, -9.33-42.54) compared with the baseline value, but this improvement was not statistically significant (p= 0.21). However, cadence significantly improved by 1.30 steps (95% confidence interval, 0.17-2.42; p=0.02).

Conclusion Long-term, repetitive HAL treatments may help patients with ALS maintain their gait.

Key words: amyotrophic lateral sclerosis, hybrid assistive limb, cyborg robot, rehabilitation, gait ability

(Intern Med 61: 1479-1484, 2022)
(DOI: 10.2169/internalmedicine.8030-21)

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal progressive neurodegenerative disease that presents with various symptoms, such as muscle weakness, dysphagia, dysarthria, and respiratory failure. Riluzole and edaravone are the only approved drugs available for ALS that are known to delay the progression of the disease (1, 2). As ALS remains incurable, patient care is focused on the management of symptoms. Rehabilitation is an important process for maintaining the physical function during the rapid progression of the disease. Carreras et al. reported that moderate endurance exercise increased the survival in a superoxide dismutase 1 mouse model of ALS (3). Drory et al. suggested that in humans, moderate exercise could reduce the ALS Functional Rating Scale (ALS-FRS) score when compared with the usual physical activity associated with daily living (4). Rehabilitation plays an important role in patients with ALS, as it maintains the physical function and quality of life. Weak-

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Received for publication May 26, 2021; Accepted for publication September 1, 2021

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Figure 1. Gait training using HAL. HAL: hybrid assistive limb

ness in the lower limbs imposes limitations on movement, as well as fatigue and pain, resulting in reduced opportunities for social participation.

To provide patients with gait support, various assistive robots have been developed. The hybrid assistive limb (HAL; CYBERDYNE, Tsukuba, Japan) system is the world's first cyborg-type wearable robot that supports gait training based on the wearer's intended motion. HAL detects bioelectrical signals (BESs) on the skin surface and provides support to the wearer's voluntary drive. Although the effectiveness of HAL in stroke (5-11), spinal cord injury (12-14), cerebral palsy (15, 16), and other diseases that cause walking disability (17-19) has been reported, its use for patients with ALS has not been sufficiently investigated (20-22).

The present study therefore evaluated the effects of long-term HAL treatment in patients with ALS.

Materials and Methods

This single-center, baseline-controlled observational study was conducted at the Department of Neurology and the Department of Rehabilitation Medicine, Toho University Omori Faculty of Medicine (Tokyo, Japan). This study was approved by the Ethics Committee of Toho University Omori Medical Center. Written informed consent was obtained from all participants.

Patients

In this study, we assessed three patients diagnosed with ALS (according to the updated Awaji criteria of ALS) (23) by board-certified neurologists in our department between January and December 2019. The inclusion criteria were (i) ≥18 years old, (ii) an unsteady gait with the ability to walk for >10 m with assistance from caregivers and/or a walker, (iii) a stable gait ability for the past 3 months, (iv) the ability to fit in the robotic HAL suit (height, 150-190 cm; weight, 40-100 kg), and (v) no history of dementia. The exclusion criteria were (i) communication difficulties owing to impaired consciousness and/or cognitive dysfunction [mini-mental state examination (MMSE) score <20 points]; (ii) difficulty performing gait training exercises owing to severe dyspnea, heart disease, or orthopedic disease; (iii) serious hepatic/renal failure; (iv) gait impairment because of cerebral or muscle disorders other than ALS; (v) a history of starting new treatment, including gait training rehabilitation programs, within the month prior to study initiation, or treatment with steroids except for inhalational and topically administered medicines, or treatment with riluzole, sodium valproate, and other drugs for controlling the progression of ALS; (vi) a history of bruises, bone fracture, trauma, or other diseases that required hospitalization within 3 months prior to the commencement of this study; (vii) pregnancy or trying to get pregnant; and (viii) an inability to attach HAL sensor pads to the skin.

Gait training program

The gait training program using HAL was conducted by two physiotherapists and a physician who had completed a safe training course for HAL. The HAL treatment consisted of treatment for at least 4-5 weeks, according to the patients' condition, with 2-3 sessions of 20- to 40-minutes duration conducted each week; only 1 session was conducted per day. One course of HAL treatment consisted of 9-10 sessions for at least 4 weeks. The period between courses was at least two months, and patients underwent conventional gait training without HAL and conventional physical therapy during this period.

Gait training was conducted on a motor-driven treadmill with a bodyweight support harness system to prevent falls. Training started with the Cybernic Voluntary Control mode based on the BES generated by motor unit activities, which were detected from electrodes placed on the patients' skin surface of the iliopsoas, quadriceps, hamstrings, and gluteal muscles. The settings were adjusted according to the severity of each patient's individual muscle dysfunction to allow them to easily move their lower extremities. During training, the physiotherapist checked the BES and adjusted the motor-assist level for each patient. For safety reasons, support of the handrail of the treadmill and a walking device with a harness were used during training, and two physiotherapists supported the patients to keep them from falling. If patients experienced respiratory discomfort during training or fatigue and muscle pain on the day following training, the treadmill speed and training time were adjusted appropriately (Fig. 1).

Demographic data and outcome measures

Baseline measures included demographic data pertaining to the following: lesion of onset; duration of the disease; presence of riluzole prescription, percutaneous gastrostomy (PEG), or noninvasive ventilation (NIV); MMSE score; ALS Functional Rating Scale-Revised (ALSFRS-R) score; and forced vital capacity (% FVC). The gait ability (2-minutes walk distance along with gait speed, step length, and cadence in the 10-m walk test), ALSFRS-R, and % FVC were assessed prior to the start of HAL treatment in each course. Gait ability tests were conducted by physiotherapists trained

Table 1. Baseline Characteristics.

Variable	Case 1	Case 2	Case 3
Sex	Female	Female	Female
Age	60	69	81
Onset lesion	Lower extremities	Upper extremities	Upper extremities
Diagnosis level	Probable-laboratory supported ALS	Probable-laboratory supported ALS	Probable ALS
Duration (months) from onset	82	98	47
Riluzole prescription	Yes	Yes	Yes
PEG†	None	None	None
NIV‡	None	None	None
MMSE§	30/30	30/30	30/30
ALSFRS-R¶	45	40	37
% Forced vital capacity	122.1	103	99

†Percutaneous gastrostomy; ‡Noninvasive ventilation; §Mini-mental state examination; ¶ALS Functional Rating Scale-Revised

ALS: amyotrophic lateral sclerosis, ALSFRS-R: ALS Functional Rating Scale-Revised

to perform standardized assessment procedures.

Outcome measures were obtained by subtracting the initial value from the value after the intervention. A multiple regression analysis was performed by adding the baseline value, each participant's ID, and time point as covariates. All statistical analyses were performed using the SAS software program, ver. 9.40 (SAS Institute; Cary, USA), and statistical tests were two-sided. The level of significance was set at $p<0.05$.

Results

Details of patient characteristics are summarized in Table 1. All three patients met the study criteria and were included in the study; there were no dropouts during this prospective observational study. One patient's onset was in the lower extremities, and two patients' onset was in the upper extremities. None of the patients underwent PEG or NIV. All three patients were assessed using the MMSE, and none had cognitive dysfunction. The average period from the baseline to the end of the 3 courses was 319.7±33.7 days. On the 2-minutes walk test, the average walking distance at baseline was 104.86 (range, 84.7-132.9) m, which improved to 111.5 (range, 56.3-161.1) m after 3 courses of HAL training (Fig. 2). The results of the 10-m walk test are presented in Table 2.

A multiple regression analysis showed that HAL treatment significantly improved the cadence by 1.30 steps (95% confidence interval, 0.17-2.42; $p=0.02$). We also performed an analysis excluding patient 3 because of her age. The corresponding p-values for the 2-minutes walk test, speed, step length, step cadence in 10-m walk test, % FVC, and ALSFRS-R were then $p=0.2111$, $p\leq0.0001$, $p=0.0004$, $p=0.1034$, $p<0.001$, and $p=1.0000$, respectively. These findings showed that by excluding one sample, the results became ambiguous because of the limited sample size.

Discussion

This study demonstrated the effectiveness of long-term HAL use in maintaining gait in patients with ALS. We found that cadence significantly improved in the 10-m walk test. Similarly, improvements in the distance achieved in the 2-minutes walk test were observed in all patients, although not significant. Other measures, such as the ALSFRS-R scores and % FVC, were relatively maintained given the rapid progression of the disease. These data indicated a trend that HAL treatment maintained gait ability in ALS patients.

In neuromuscular diseases, such as ALS, overactivity of upper motor neurons increases the synaptic stimuli to spinal motor neurons to maintain muscle strength, which may accelerate the degeneration of motor neurons. In recent years, the existence of neuroplasticity has been reported (24, 25) However, whether or not neuroplasticity occurs in neurodegenerative disorders, such as ALS, remains unclear. If each motor unit could be specifically stimulated according to the degree of motor unit degeneration, symptoms might improve, and the rate of degeneration might be reduced. HAL is based on a technology called "cybernics," in which devices and the body are electrically and mechanically connected, and information is exchanged to support movements. Sankai et al. proposed that HAL might activate neuroplasticity through repetitive and accurate movements (26). HAL training allows the wearer to walk repeatedly and intentionally in an errorless pattern without causing fatigue or adverse effects. It is based on Edelman's theory, which states that highly-activated neuron networks tend to be selected (27), and on the Hebbian theory, which proposes that frequently used neural circuits aid in their strengthening (28). The present study found that long-term training with HAL was effective in inducing neuroplasticity and maintaining the ability to walk in patients with ALS. HAL gait training may also maintain the function and improve

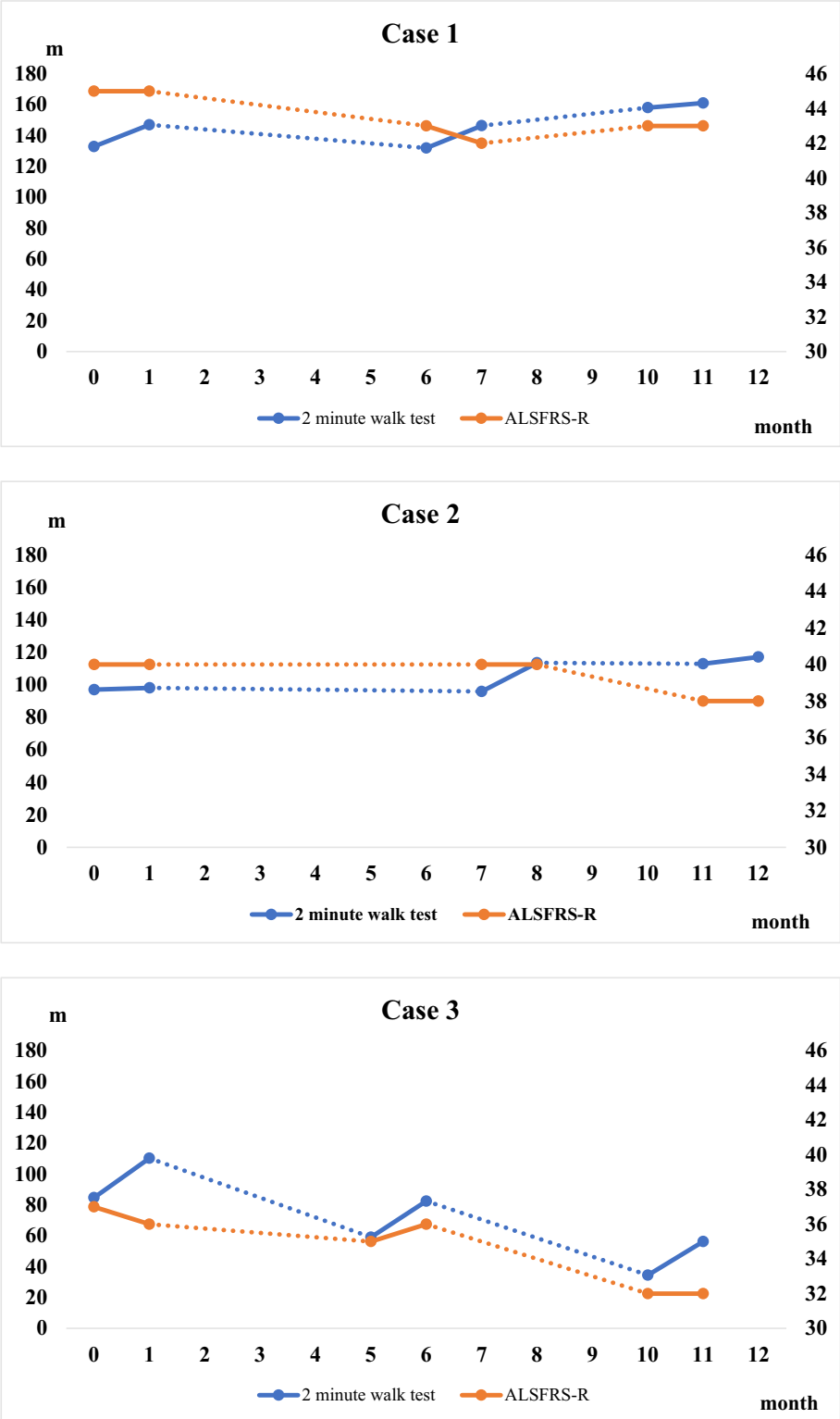

Figure 2. Time course of the 2-minute walk distance and the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score.

patient-reported outcomes, as the 3 participants were able to continue the training for an average of 10 months without dropping out.

Several limitations associated with the present study warrant mention. It was a single-arm observational study with a small number of cases. There was no control group of patients treated using only conventional physical therapy without HAL. Well-designed controlled studies, followed by larger studies using qualitative approaches, are needed to explore the effect sizes and the effect on the quality of life. Validation of upper and lower neuron signs in each patient with ALS may provide results different from those presented in this study. A further evaluation related to the adaptation criteria for patients with ALS is needed.

Table 2. Difference from Baseline in Outcome Data.

n=3	Baseline Mean, range	After three courses Mean, range	Mean difference 95% confidence interval	p value
2-minutes walk test (m)	104.867 84.7-97	111.5 56.3-161.1	16.61 -9.33-42.52	0.21
ALSFRS-R	40.6667 37-45	37.333 27-43	-0.15 -0.49-0.19	0.39
Gait speed (m/s)	1.268 1.071-1.705	1.084 0.524-1.622	0.30 -0.60-1.20	0.52
Step length (m/step)	0.564 0.545-0.6	0.547 0.375-0.667	-0.25 -0.54-0.04	0.10
Cadence (step/s)	2.136 1.887-2.557	1.892 1.399-2.432	1.30 0.17-2.42	0.02
% Forced vital capacity	108.033 99-122.1	109.433 98.1-120.8	-1.24 -2.96-0.48	0.16

ALSFRS-R: ALS Functional Rating Scale-Revised
*Multiple regression analysis

Conclusion

ALS is an incurable, fatal disease that usually progresses rapidly. Our study showed that long-term repetitive gait training with HAL can preserve the gait function for at least 10 months in patients with ALS. New drug treatments are expected to be developed in the future, and combining such treatments with HAL training may dramatically change the clinical outcomes of ALS.

The authors state that they have no Conflict of Interest (COI).

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