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Factors Leading to Improved Gait Function in Patients with Subacute or Chronic Central Nervous System Impairments Who Receive Functional Training with the Robot Suit Hybrid Assistive Limb

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Abstract

The factors that lead to the improvement of gait function in patients with diseases of the central nervous system (CNS) who use a hybrid assistive limb (HAL) are not yet fully understood. The purpose of the present study was to analyze these factors to determine the prognosis of the patients' gait function. Patients whose CNS disease was within 180 days since onset were designated as the subacute-phase patients, and patients whose disease onset had occurred more than 180 days previously were designated as chronic-phase patients. Fifteen subacute-phase patients and 15 chronic-phase patients were given HAL training. The study analyzed how post-training walking independence in these patients was affected by the following factors: age, disease, lesion area, lower limb function, balance, period until the start of training, number of training sessions, additional rehabilitation, higher-order cognitive dysfunction, HAL model, and the use of a non-weight-bearing walking-aid. In subacute-phase patients, walking independence was related to lower limb function ($r_s = 0.35$). In chronic-phase patients, there was a statistically significant correlation between post-training walking independence and balance ($r_s = 0.78$). In addition, in patients with a severe motor dysfunction that was accompanied by inattention and global cognitive dysfunction, little improvement occurred, even with double-leg model training, because they had difficulty wearing the device. The results demonstrated that the factors that improved walking independence post HAL training differed between patients with subacute- and chronic-stage CNS diseases. The findings may serve as valuable information for future HAL training of patients with CNS diseases.

Key words: gait function, hybrid assistive limb, neurorehabilitation, central nervous system disease

Introduction

Walking is an important ability for everyday living, and for humans, it provides a high degree of freedom to respond to changes in the environment. Most patients with central nervous system (CNS) diseases experience motor paralysis of the lower limbs, and their gait function is impaired, which restricts movement in daily life.

In recent years, various gait training assistive robots have been developed, such as the Rehabot,[1)] Gait Trainer,[2,3)] Lokomat,[4)] and LOPES Exoskeleton Robot,[5)] and rehabilitation using robots is becoming more widespread. The hybrid assistive limb ([HAL], CYBERDYNE, Inc., Tsukuba, Japan) is a cyborg-type gait-assistive robot that was developed by Sankai et al.[6,7)] to assist with walking. It features a voluntary control function that complies with the wishes of the wearer, a function that was developed through the fusion of medicine and engineering. HAL is a new type of neurorehabilitation tool that supports the automatic movement of the hip and knee joints based on the bioelectrical signals (BES) from the wearer's rectus femoris, vastus lateralis, biceps

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femoris, and gluteus maximus. Simultaneously, this suit uses information on the position of the center of gravity to determine the stance or swing phases, possesses functions that detect voluntary human movement, and offers a technological, automatic control capability to support the movement of the lower limbs in synchronization with the gait cycle.

Gait training with the gait-assistive robot suit HAL has been reported to improve the walking ability of patients with either acute[8–10] or chronic stroke,[11] or spinal cord injury,[12,13] and effectively reduces the amount of assistance during the wearer's activities of daily livings (ADLs).[14] However, there is little information on the application of HAL to rehabilitate patients with gait disorders and CNS diseases such as stroke, brain tumor, and spinal cord injury. Therefore, uncovering the factors affecting the prognosis of patient function, particularly patient characteristics such as age, disease, disease site, cognitive dysfunction, lower limb function, balance, and intervention period, will likely provide valuable information when considering how to apply HAL training.

The purpose of this study was to analyze the factors affecting the prognosis of gait function after HAL training in patients with CNS diseases.

Materials and Methods

The gait disturbance was due to intracerebral hemorrhage in 15 patients, cerebral infarction in 4, meningioma in 5, diffuse axonal injury in 3, and spinal cord disease in 3, with a consciousness level of grade 1 or grade 0 on the Japan Coma Scale (JCS).[15] The study was approved by the ethical committee of the University of the Ryukyus (No. 377), and training using HAL was provided to 30 patients who were given a written explanation about their cooperation in the study and from whom informed consent to participate was obtained. We classified patients who had started HAL training within 180 days since the onset of disease into the subacute-phase group, and those who started HAL training after at least 180 days since disease onset were classified into the chronic-phase group.[16,17] The subacute group (cases 1–15) consisted of 10 women and 5 men with a median age of 61 years (range: 18 to 86 years). All patients in the subacute-phase group had a lower limb deficit and gait disorder. The chronic group (cases 16–30) consisted of 3 women and 12 men with a median age of 59 years (range: 19 to 83 years). All patients in the chronic-phase group had a lower limb deficit, and 11 patients in this group had a gait disorder. The details of each patient's profile are given in Table 1.

HAL training was conducted for 30 minutes once daily. The time required to put on or remove the HAL was not included in the training time. The HAL training program consisted of sitting balance, standing balance, and gait training. Training was conducted with patients wearing either a single-leg or double-leg HAL model. Patients with paraplegia or quadriplegia and/or patients who could not maintain a sitting position used the double-leg HAL model. The single-leg HAL model was applied to patients with hemiplegia who could maintain a sitting position.[18] Patients who could not maintain a sitting or standing position used an All-in-One Walking Trainer (All-in-One, manufactured by ROPOX A/S, Næstved, Denmark). A dedicated sling (DOMINO Slings, manufactured by ROPOX A/S) for the All-in-One was used, and because it could support the pelvis of the wearer and hold up the trunk of the body, it even allowed patients who were unable to maintain a seated or standing position to do so safely.

Gait function, lower limb function, balance, and ADLs were each evaluated according to the Functional Ambulation Categories (FAC),[19]

Table 1 Clinical features of the patients in this study

Case	Age	Sex	Diagnosis	Location	Type of paralysis	Higher-order cognitive dysfunction	Period from the onset (days)	Type of HAL
Case 1	80	M	olfactory groove meningioma	frontal	paraplegia	global cognitive function	25	double
Case 2	86	F	falx meningioma	parietal	hemiplegia	executive function	8	single
Case 3	61	F	parasagittal meningioma	frontal	hemiplegia	executive function, phycomotor speed	26	single
Case 4	57	F	ICH	frontal	hemiplegia	-	16	double
Case 5	69	F	ICH	putamen	hemiplegia	transcortical motor aphasia	8	double

(*Continued*)

Table 1 (Continued)

Case	Age	Sex	Diagnosis	Location	Type of paralysis	Higher-order cognitive dysfunction	Period from the onset (days)	Type of HAL
Case 6	55	M	ICH	thalamus	hemiplegia	-	4	single
Case 7	62	F	ICH	parietal	hemiplegia	-	5	single
Case 8	38	F	ICH	putamen	hemiplegia	transcortical motor aphasia	8	single
Case 9	51	F	SAH	insular	hemiplegia	executive function, pusher behavior	21	double
Case 10	72	F	cerebral infarction, schizophrenia	frontal, parietal, putamen, temporal, insula	hemiplegia	unilateral spatial neglect	22	double
Case 11	76	M	cerebral infarction	cerebral peduncle, cerebellum	hemiplegia	-	15	single
Case 12	18	M	DAI	orbitofrontal, parietal, temporal pole	hemiplegia	phycomotor speed, working memory	79	single
Case 13	74	F	petroclival meningioma, cerebral infarction	brain stem	hemiplegia	-	20	single
Case 14	52	M	cerebral infarction	corona radiate	hemiplegia	-	16	single
Case 15	61	F	ICH	parietal	hemiplegia	constructional apraxia	21	single
Case 16	83	M	parasagittal meningioma	frontal	hemiplegia	-	13149	single
Case 17	53	F	ICH	putamen	hemiplegia	-	801	single
Case 18	60	M	ICH	putamen	hemiplegia	transcortical motor aphasia	237	single
Case 19	61	M	ICH	thalamus	hemiplegia	-	858	single
Case 20	60	F	ICH	parietal	hemiplegia	motor aphasia	592	single
Case 21	40	M	ICH	insula	hemiplegia	motor aphasia	5844	single
Case 22	57	M	ICH	putamen	hemiplegia	transcortical motor aphasia	763	single
Case 23	64	F	ICH	frontal	hemiplegia	motor aphasia	609	single
Case 24	75	M	ICH	thalamus	hemiplegia	executive function, phycomotor speed	2708	single
Case 25	59	M	cerebral infarction	frontal, parietal, putamen, insula	hemiplegia	transcortical motor aphasia	4078	single
Case 26	22	M	DAI	corpus callosum, corona radiata (R), temporal (L), occipital (L)	quadriplegia	global cognitive function	413	double
Case 27	19	M	DAI	corpus callosum, corona radiata, cerebellar vermis	hemiplegia	working memory	586	single
Case 28	69	M	spinal cord injury	C5, C6	quadriplegia	executive function, working memory	2464	double
Case 29	50	M	syringomyelia	C1～T5	quadriplegia	-	2246	double
Case 30	44	M	dural AVF	T6～T8	hemiplegia	-	1403	single

AVF: arteriovenous fistula, C: cervical nerves, DAI: diffuse axonal injury, double: double-leg model with exoskeleton frame, F: female, HAL: hybrid assistive limb, ICH: intracerebral hemorrhage, M: male, single: single-leg model with exoskeleton frame, SAH: subarachnoid hemorrhage, T: thoracic nerves.

Fugl-Meyer Assessment (FMA),[20] and Functional Independence Measure (FIM)[21,22] before HAL training started and when it was finished.

The neuropsychological assessments that were used are shown below. The Mini-Mental State Examination (MMSE)[23] and a modified MMSE (3MS)[24] were used for the global cognitive screening assessment. The flexibility of the executive function of the frontal lobe was evaluated with the Trail Making Test (TMT),[25] and cognitive inhibition was evaluated with the Stroop Test (ST).[25] The Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit span subtest (DS),[26] which reveals the retention operation of working memory, was used to evaluate memory function. Furthermore, the WAIS-R digit symbol test (DST)[26] was used to evaluate the psychomotor speed of the entire brain. To evaluate the visuospatial ability of the parietal lobe, we used a partial WAIS-R block design subtest[26] and the cube-copying test.

Spearman's rank-order correlation analysis was used to calculate correlations between the FAC when HAL training was finished and age, the period from disease onset until the start of training, number of training sessions, and scores of lower limb function and balance before training. The range of the rank-order correlation coefficient (r_s) was between –1 and +1. When the r_s value was close to +1, it indicated that there was a positive correlation between the FAC and scores of the other functional assessment items. Conversely, when the r_s value was close to −1, there was a negative correlation between the FAC and other functional assessment items. The strength of the r_s value was assessed using five categories: negligible correlation (0.00 to 0.30 or 0.00 to −0.30), low correlation (0.30 to 0.50 or −0.30 to −0.50), moderate correlation (0.50 to 0.70 or −0.50 to −0.70), high correlation (0.70 to 0.90 or −0.70 to −0.90), and very high correlation (0.90 to 1.00 or −0.90 to −1.00).[27,28] If the strength of the r_s value was more than 0.3, it was considered to be positively correlated, and if it was less than −0.3, it was considered to be negatively correlated. Fisher's exact test was used to test the significance between the number of patients who were capable (FAC > 1) and incapable of walking (FAC = 0) when HAL training was finished, according to seven factors: (1) lesion side, (2) disease type, (3) lesion site, (4) presence or absence of higher-order cognitive dysfunction, (5) HAL specification, (6) additional use of the All-in-One, and (7) additional occupational therapy (OT) or physical therapy (PT) (significance level: 5%). In addition, the Wilcoxon rank-sum test was used to assess the difference in the median values of FAC, FMA (lower limb function and balance), and FIM before HAL training started and when it was finished (significance level: 5%).

Results

HAL training was provided to 15 patients with subacute-phase CNS disease and 15 patients with chronic-phase disease. The details of each group are given in Table 2.

All functional assessments in the patients with subacute-phase disease and the those with chronic-phase disease showed that there was improvement. The patients whose disease was in the subacute phase demonstrated a significant increase ($P < 0.01$)

Table 2 Summary of patients' characteristics

Characteristics	Subacute phases		Chronic phases	
	$n = 15$	%	$n = 15$	%
Higher-order cognitive dysfunction				
yes	8	53%	8	53%
no	7	47%	7	47%
Period from the onset to starting training	13		858	
(range)	(5–79)		(237–13149)	
Number of training sessions (median)	5		5	
(range)	(5–15)		(5–10)	
Specification of HAL				
single-leg model	10	67%	12	80%
double-leg model	5	33%	3	20%
Application of All-in-one				
yes	10	67%	6	38%
no	5	33%	9	56%
Application of OT or PT				
yes	15	100%	1	7%
no	0	0%	14	93%
FAC before HAL training				
FAC ≥ 1	0	0%	12	80%
FAC = 0	15	100%	3	20%

FAC: functional ambulation classification, HAL: hybrid assistive limb, OT: occupational therapy, PT: physical therapy. The integer denotes the number of patients.

in the median FAC score from 0 ± 0 (range: 0–0) before training started to 2 ± 1 (range: 0–4) when training was finished (Fig. 1A). The walking categories in the chronic phase group significantly increased ($P < 0.01$) from baseline (median: 3 ± 1; range: 0–5) to after training (median: 4 ± 1.8; range: 0–5) (Fig. 1A). The median score for lower limb function in the subacute and chronic-phase groups significantly improved from before training (5 ± 4.5; range: 1–14) to after training (21 ± 5.9; range: 9–29, $P < 0.001$), and from 17 ± 5.9 (range: 4–25) to 22 ± 5.5 (range: 9–27, $P < 0.001$), respectively (Fig. 1B). The balance scores of the FMA in the patients whose disease was in the subacute phase significantly increased ($P < 0.001$) from baseline (median: 1 ± 0.7; range: 0–2) to when training was finished (median: 7 ± 2.7; range: 2–11) (Fig. 1C). A significant increase ($P < 0.001$) in the median score for balance from 8 ± 3.8 (range: 0–11) to 11 ± 3.9 (range: 3–13) was observed in the patients whose disease was in the chronic phase (Fig. 1C). The median scores for ADLs in patients in both the subacute and chronic-phase groups showed a significant improvement ($P < 0.001$) from 49 ± 14.2 (range: 28–70) to 82 ± 20.2 (range: 40–104), and from 100 ± 25.7 (range: 34–120) to 105 ± 24.2 (range: 45–121), respectively (Fig. 1D).

In the subacute-phase group, Fisher's exact test revealed that there was no significant bias in the number of patients who were capable (FAC ≥ 1) and incapable of walking (FAC = 0) after training (Table 3). In the chronic-phase group, Fisher's exact test showed that there was a significant bias in the number of patients who were capable and incapable of walking after training, according to the affected side ($P < 0.05$) and the HAL specification that was used for training ($P < 0.05$) (Table 3). These results showed that bilateral-side lesions and training with the double-leg HAL model affected gait function after HAL training in patients with chronic-phase disease.

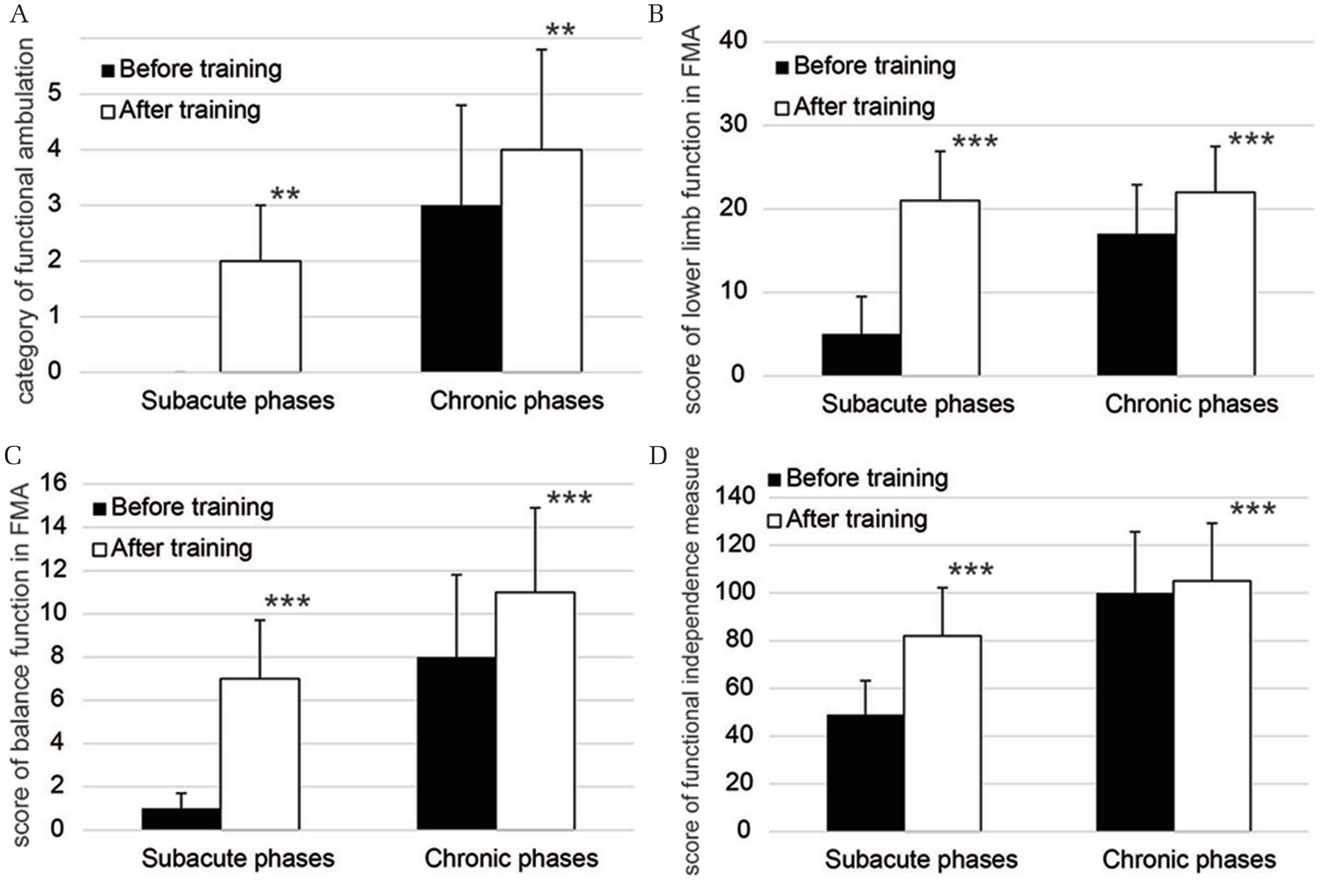

Fig. 1 Change in functional assessments of the patients in the subacute-phase disease group and chronic-phase disease group. The bar graphs show the median scores for the functional ambulation category before HAL training and after HAL training (A). The bar graphs illustrate the median scores for lower extremity function in the Fugl-Meyer assessment (FMA) (B). The bar graphs demonstrate the median scores for balance in the FMA (C). The bar graphs show the median scores of functional independent measure (D). ** and * denote $P < 0.01$ and $P < 0.001$, respectively (the Wilcoxon rank-sum test).**

Table 3 Clinical factors influenced on gait function after HAL training finished

Factor	Subacute phases		P	Chronic phases		P
	FAC = 0	FAC ≥ 1		FAC = 0	FAC ≥ 1	
Side of lesion			0.64			0.03
Left	1	4		0	7	
Rgiht	1	8		0	5	
Bilateral	0	1		2*	1	
Diagnosis			0.61			0.2
intracerebral hemorrhage	1	6		0	8	
cerebral infarction	1	2		0	1	
meningioma	0	4		0	1	
diffuse axonal injury	0	1		1	1	
spinal cord diseases	0	0		1	2	
Location of lesion			0.88			0.64
frontal lobe	1	4		0	4	
parietal lobe	1	4		0	2	
temporal lobe	1	1		0	0	
insula cortex	1	1		0	2	
putamen	1	2		0	4	
thalamus	0	0		0	2	
corpus callosum	0	0		1	1	
corona radiata	1	1		1	2	
brainstem	0	2		0	1	
cerebellum	0	1		0	1	
spinal cord	0	0		1	2	
Higher-order cognitive dysfunction			0.28			0.5
yes	2	8		2	8	
no	0	5		0	5	
Specification of HAL			0.09			0.03
single-leg type	0	10		0	12*	
double-leg type	2	3		2*	1	
Application of All-in-one			0.09			0.18
yes	0	10		2	4	
no	2	3		0	9	
Combination of OT or PT			1.0			1.0
yes	2	13		0	1	
no	0	0		2	12	

FAC: functional ambulation classification, FAC = 0: number of patients who cannot ambulate, FAC ≥ 1: number of patients are classified as from 1 to 5 in FAC, HAL: hybrid assistive limb, OT: occupational therapy, PT: physical therapy, *P*: *P*-value of Fisher's exact test, *: $P < 0.05$ (residual analysis).

Table 4 Spearman's rank-order correlation coefficients of gait function and age, period from the onset, number of training sessions, function of lower extermity and postural control before HAL training, respectively

Variables	Subacute phases	Chronic phases
Age	–0.19	–0.18
Period from the onset	–0.14	0.24
Number of training sessions	0.06	–0.28
Lower limb score of FMA before training	0.35	0.36
Balance score of FMA before training	0.24	0.78***

FMA: Fugl-Meyer assessment, HAL: hybrid-assistive limb, ***: $P < 0.001$.

The results of the Spearman's rank-order correlation analysis and FMA scores for lower limb function showed that there was a low positive correlation ($r_s = 0.35$, $P = 0.09$) with the FAC scores after HAL training in the subacute-phase patients (Table 4). The chronic-phase diseases demonstrated a high positive correlation ($r_s = 0.78$, $P = 0.003$) with the FMA scores for balance, and a low positive correlation ($r_s = 0.36$, $P = 0.09$) with the scores for lower extremity function (Table 4).

The walking categories and the lower limb function scores for individual patients whose disease was in the subacute phase are shown in Fig. 2A. The arrows show the change in gait and lower limb function from before training started to when training was finished. The patients with a lower limb function score of 8 or higher before training experienced an improvement of the FAC score to 3 after HAL training. The patients with a lower limb function score of 5 or lower before training tended to have an FAC score that improved to 2. Figure 2B shows the change in gait function and balance scores of patients in the chronic-phase group from the start of training until it was finished. The FAC of 9 patients increased by one level after HAL training was finished, and the balance scores also improved. Eight patients who had a balance score of 7 or higher before training improved to an FAC of 3 or higher when training was finished, and 5 patients, in particular, regained walking independence. After training, there was an increase in the balance scores, but there was no change in the FAC of 2 patients with an FAC of 0 and 4 patients with an FAC of 5. Four of the 15 patients who used the double-leg model (patients 5, 10, 26, and 28) remained unable to walk. Patients 5, 10, 26, and 28 had severe motor dysfunction or quadriplegia that was complicated by higher-order cognitive dysfunction.

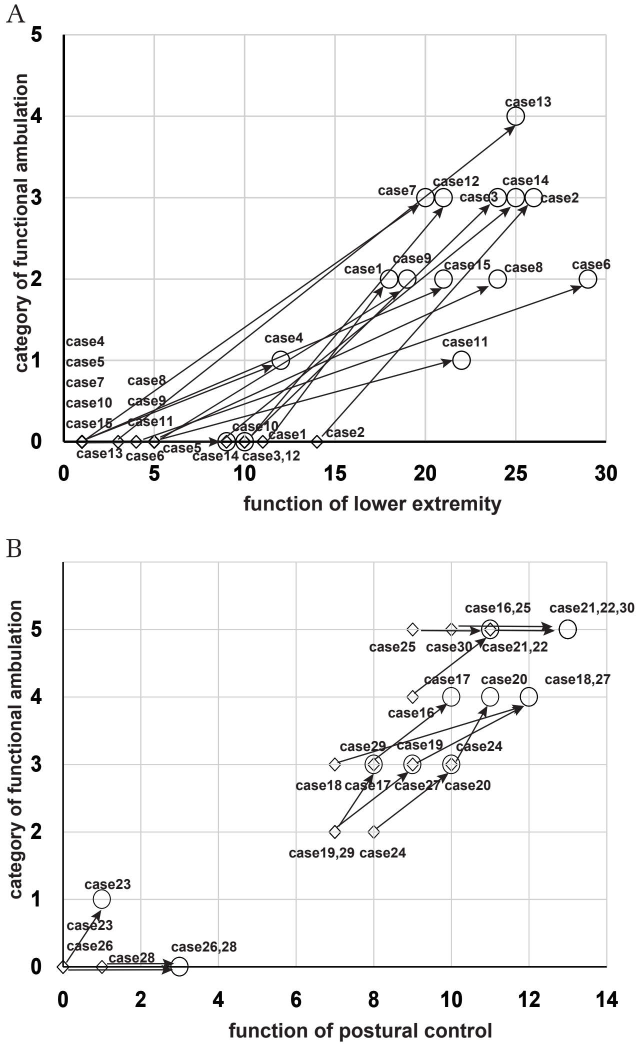

Fig. 2 Alteration of the walking category and physical function in the patients in the subacute-phase disease group and chronic-phase disease group. A scatterplot illustrates the categories of functional ambulation (y axis) and scores of lower limb function (x axis) before and after HAL training in each patient with a subacute CNS disease (A). The square and circle denote data from pre-training and post-training, respectively. The arrow represents alteration of walking ability and lower limb function in patients after HAL training. A scatterplot graph illustrates the categories of functional ambulation (y axis) and scores for postural control (x axis) before and after HAL training in each patient with a chronic CNS disease (B). The arrows represent improvement in gait function and postural control in patients after HAL training.

Discussion

The goal of this study was to analyze the factors that are related to the prognosis of gait after HAL training in patients with lower limb motor paralysis due to CNS diseases such as stroke and benign brain tumor. We analyzed the factors that affect the prognosis of gait function after HAL training in patients with subacute- and chronic-phase disease.

The traditional rehabilitation approach, neurodevelopmental treatment, and/or robotic-assisted locomotor training for patients in the acute and chronic phases of CNS disease improved their dysfunction of the lower limb and standing balance, as well as walking ability.[4,8–11,17,29,30–32] The robot-assisted training that included HAL restored the gait function and/or ADLs of patients after the subacute stage of stroke, compared with conventional rehabilitation.[4,14,16,33] There is not much difference in the walking ability and/or balance of patients in the chronic stage after stroke between rehabilitation with Locomat and the conventional rehabilitation.[31,34] Recently, several reports indicated that gait training with robot-suit HAL improved gait function and standing balance in patients in the chronic phase after stroke.[11,34,35] Our study demonstrated that HAL training improved not only the walking ability but also the function of the lower limb, balance, and ADLs of patients with CNS diseases, both in the subacute and chronic phases. Indeed, in our study, HAL training effectively improved the function of patients with the chronic stage of CNS disease, although we found that it was difficult to recover the patients' motor functioning using conventional rehabilitation.[36]

Lower limb function, represented by an FMA score of 4 or above, indicated that the tendon reflex and synergistic pattern in voluntary movement were normal.[20] The BES-induced, synergistic movement of the lower limbs is triggered using HAL gait assistance.[6,7] Although, the effect of HAL on gait function in patients with mild motor paralysis has been reported,[8] in this study, we found that starting HAL training soon after CNS disease onset or an operation led to effective improvement of gait disorders in patients with severe motor paralysis.

The double-leg HAL model is an effective tool for the gait training of patients with paraplegia or quadriplegia with a spinal cord injury and/or severe brain injury.[10,18,34] Patients with global cognitive dysfunction and inattention remained unable to walk in this study, and could not be expected to improve their walking ability.[37,38] For the double-leg HAL model to work, the wearer must use knee or hip joint movements such as bending and elongation in both legs; therefore, compared with the single-leg type model, attention must be paid to more joints, and more movement control is required.[6,7]

The stability of standing balance is closely associated with the stance phase of a bipedal gait cycle.[39–43] In each step, the patient must be able to adjust the posture of the head and body so that the body's center of gravity (CG) does not fly out from the base of support.[40,41,44] HAL supports the movement of the lower limbs,[6,7] but the postural adjustment of the head and body depends mostly on the ability of the wearer. Patients with good standing balance may experience improvements in their walking ability because the HAL training facilitates forward propulsion of the CG and alignment of the lower limb during the stance phase.[6,7,45]

This study had several limitations. Firstly, this was a retrospective study, and it was not randomized or double-blinded. Next, the number of patients with subacute- or chronic-stage disease was very small. We plan to perform a randomized double-blind study with a larger number of subjects to have solid proof of the utility of HAL for training. The factors that help improve the effect of HAL training on lower limb function and balance must be further analyzed.

In conclusion, we found that the walking ability of patients with CNS disease after HAL training was influenced by lower limb function, standing balance, and higher-order cognitive dysfunction. These findings are valuable for predicting the prognosis of gait function after HAL training in patients with a CNS disease and for considering the application of HAL to rehabilitation.

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Conflicts of Interest Disclosure

None declared. All authors who are members of The Japan Neurosurgical Society (JNS) have registered self-reported COI disclosure statement forms through the website for JNS members.

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