EFFECT OF GAIT TRAINING USING HYBRID ASSISTIVE LIMB ON GAIT ABILITY AND THE RISK FOR OVERWORK WEAKNESS IN THE LOWER LIMB MUSCLES IN PATIENTS WITH NEUROMUSCULAR DISEASE: A PROOF-OF-CONCEPT STUDY

（神経筋疾患患者に対するHybrid Assistive Limbを用いた歩行訓練の効果と過用性筋力低下リスクの検討：実証研究）

申請者：　弘前大学大学院医学研究科
機能再建・再生科学領域
リハビリテーション医学教育研究分野
氏名：　古川　正和
指導教授：　津田　英一

ABSTRACT

BACKGROUND: Few previous studies have reported the efficacy of robot rehabilitation for improving gait ability or its adverse events in patients with neuromuscular diseases.

AIM: The aim of the present study was to elucidate the effects of gait training with a hybrid assistive limb (HAL) on gait ability and to investigate serum enzyme levels associated with skeletal muscle damage.

DESIGN: Proof-of-concept study.

POPULATION: Twenty-one patients with neuromuscular disease (NMD, 13 males and 8 females, mean age of 60.6 years).

SETTING: Department of rehabilitation medicine in university hospital.

METHODS: All patients underwent 1 to 7 series of gait rehabilitation which consisted of 9 sessions of HAL training. Gait ability was assessed with the 10-meter walk test and the 2-min walk test before and after HAL training, while serum creatine phosphokinase, aspartate aminotransferase, and lactic acid dehydrogenase values were measured before, midway through, and after HAL training.

RESULTS: Gait velocity and step length for 10-meter walk test, and 2-min walk distance were significantly improved after HAL gait training. There was no significant change in serum level of all 3 measured enzymes between the three time points.

CONCLUSIONS: HAL gait training with the practical setting as this study improved gait ability in patients with progressive NMD and did not damage skeletal muscle, as indicated by no significant change in serum level of muscle enzymes.

CLINICAL REHABILITATION IMPACT: Robot assisted gait training could be safely applied to the patients with NMD, as one of the effective rehabilitation programs to improve gait ability.
(*Cite this article as:* Kogawa M, Miura K, Yasuda K, Ishibashi Y, Tsuda E. Effect of gait training using Hybrid Assistive Limb on gait ability and the risk for overwork weakness in the lower limb muscles in patients with neuromuscular diseases: a proof-of-concept study. DOI: 10.23736/S1973-9087.21.06387-5)

Key words: Rehabilitation; Robotics; Walking.

Neuromuscular disease (NMD) affects the functioning of muscles due to nerve, muscle, and neuromuscular junction pathology, and most of them are progressive in the natural course. And thus, the patients with NMD gradually result in impaired activities of daily living and an inferior quality of life. National Database (NDB) open-source data from 2018 generated by the Ministry of Health, Labor and Welfare in Japan demonstrated that more than 250,000 patients received medical treatments for NMDs from January to December 2017 in Japan.[1] To address this need, medical innovations have led to novel treatment modalities for many previously intractable diseases.

However, effective treatments for the underlying pathology or that inhibit the progression of NMDs remain elusive.

The same problem remains relevant to rehabilitation for NMDs, as it is difficult to improve physical impairments to meet the traditional goals of rehabilitation, which include overcoming functional disabilities or social handicaps to maximize quality of life.[2] The conventional rehabilitation for NMDs consists of relaxation, stretching, passive and active range of motion exercises, low dose strengthening exercises, and ambulatory and activity of daily life trainings. Also, compensatory approach is frequently utilized, accompanied by employing a walking-aid or wheelchair and adapting living and work environments to the patient's disability. Clinical studies of the efficacy of rehabilitation exercises for improving physical function in patients with NMD have had mixed results. One review concluded that exercise likely improves function,[3] whereas others have reported more equivocal results.[4] Thus, there remains no comprehensive recommendations on rehabilitation for regaining and/or maintaining gait in patients with NMD.

To improve gait in a rehabilitation context, various robotic devices have been developed and are commercially available. Recent clinical studies have examined the effects of gait training using robotic devices, such as Lokomat (Hocoma, Switzerland), LOPES (University of Twente, Twente, Netherland), ReWalk (Robotics, Hertzliya Pituach, Israel) and Indego (Parker Hannifin Corporation, Fort Worth, TX, USA). These devices promote the repetitive, accurate, and reproducible practice of normal gait patterns, as well as task-specific training. Lokomat is a robotic treadmill training system that uses a body weight support system to suspend individuals and robotic legs that assist with basic walking functions.[5] The robotic legs were composed by actuator and the orthosis, with position sensors and force sensors that allow real-time monitoring of the position of the joints and the forces involved during the gait training session, enabling to regulate and control the amplitude of movement of the hip and knee. LOPES is also designed for use in training on a treadmill, and combines a freely translatable and two-dimensional actuated pelvis segment with a leg exoskeleton containing actuated rotational joints at the hip and knee joint.[6] The LOPES makes a forward stepping motion and maintains the fundamental stability during standing and walking, with interaction control based on position sensing combined with force actuation. ReWalk was a powered exoskeleton to walk over-ground in combination of with Lofstrand crutches.[7] When initiating a step, a tilt sensor on the pelvic band of the device detects the trunk movement according to the setting predetermined by the trainer. Indego has powered movements at the hip and knee joints along with embedded sensors and self-controllers.[8] It has built-in carbon fiber ankle-foot orthoses that provide ankle stability and transmit the weight of the leg orthoses to the ground. The Indego has two types of exoskeleton device with different concept. Indego Therapy offers clinicians the ability to provide patients with individualized over-ground gait rehabilitation, while Indego Personal is a custom fit exoskeleton that provides patients with increased mobility and functional independence at home and in the community. A previous meta-analysis reported that gait training using the Lokomat device in patients within six months of spinal cord injuries significantly extended gait distance, improved leg strength, and improved functional mobility and independence as compared to conventional over-ground training.[9]

A recently-developed novel Wearable Cyborg called the hybrid assistive limb (HAL, Cyberdyne INC., Tsukuba, Ibaraki Prefecture, Japan), which uses an biosignal-controlled neuromuscular feedback system, has become available for both over-ground and treadmill training in patients

with gait disorder.[10-12] The HAL assists patients' voluntary knee and hip-joint movements. It achieves this by detecting signals from force-pressure sensors in the patient's shoes and a gyroscope on their back, while also acquiring intension based weak bioelectric signals including myographic and neuroelectronic signals from surface electrodes on the associated muscles which was placed on the gluteus major, rectus femoris, vastus lateralis and lateral hamstring. Interactive biofeedback with the HAL alters cerebral activity for each specific motion and leads to neuromodulation-based recovery from physical impairments.[13]

Highlighting the efficacy of the HAL, a systematic review revealed that gait training with the HAL in patients after a stroke or spinal cord injury promoted gait recovery and walking independence, although most of the included studies were case series with no control group.[14] Few reports have examined the effects of the HAL on gait training for NMDs, or the incidence and severity of adverse effects with HAL-based training. Because the severity of stage in patients with NMD varies widely from case to case, the HAL gait training protocol can be overloaded and cause significant fatigue. In the rehabilitation of patients with NMD, physicians and therapists should take special care to avoid overwork weakness, which is an exacerbated muscle condition caused by an excessive exercise intensity and frequency. The purpose of the present study was thus to examine the effect of HAL gait training on gait ability by measuring several gait parameters, and to address HAL's safety by analyzing blood levels of muscle degeneration markers in NMD patients. We hypothesized that HAL gait training would significantly gain several gait parameters in walk tests, without significant elevation of serum muscle enzyme when conducted with a controlled intensity and frequency.

Materials and methods

Participants

The patients, who were introduced from Department of Neurology to Department of Rehabilitation Medicine in order to physical therapies for NMDs, were involved in this study. Twenty-one patients were included, all of whom were able to walk with or without a cane or walker and were referred for gait training with HAL. Thirteen male and 8 female patients with a mean age of 60.6 years (range: 39 to 84 years) and mean disease duration of 7.3 years (range: 0.5 to 24 years) were included. Eleven patients were diagnosed with amyotrophic lateral sclerosis (ALS), 2 with spinobulbar muscular atrophy (SBMA), 1 with Charcot-Marie-Tooth disease (CMT), 5 with myotonic dystrophy (MD), and 2 with inclusion body myositis (IBM). (Table I) All patients provided written informed consent, and the study was approved by the ethics review board of the Hirosaki University, Graduate School of Medicine (EK No. 2016-266) and conducted in accordance with the tenets of the Declaration of Helsinki. All work was also conducted in accordance with the Declaration of the World Medical Association (www.wma.net).

HAL treatment

All gait trainings using HAL for medical use lower limb type and data acquisition assessing gait ability were performed in the Department of Rehabilitation Medicine of Hirosaki University Hospital. As 1 series of gait training (HAL Treatment), each patient underwent total 9 sessions of HAL gait training within a 4-week period at a frequency of 2 to 3 sessions per week. HAL gait training was conducted to be substituted for conventional gait trainings, and no patients received

any other types of ambulatory exercise. On the day without HAL training, some patients underwent occupational therapy for impairments of upper extremities. A single session of HAL gait training lasted 20-30 minutes. During gait training, patients were placed in a suspension walker (All In One Walking Trainer, Ropox A/S, Næstved, Denmark) with a safety harness for fall prevention. Two experienced physical therapists prepared and operated the HAL and walker. Surface electrodes were placed on the gluteus major, rectus femoris, vastus lateralis and lateral hamstring muscles and sent bioelectrical signals to a central processing unit. The Cybernic Voluntary Control (CVC) mode[15] was selected throughout the entirety of the HAL gait training session in all patients (Figure 1). The physical therapist adjusted the detection sensitivity appropriately for the bio-signals and tuned the extension and flexion torque generated by the hip and knee motors in each session, to maximize patient comfort. The HAL ankle joints were usually fixed in a neutral dorsi/planter flexion position. When the patient agreed, another series of HAL Treatment was conducted at an interval of more than 1 month. Depending on patient preference, several series of HAL gait trainings were repeated in this later study period (Table I).

Outcome measurement

Gait ability

Gait ability was evaluated (without use of the HAL) before and after 4 weeks of HAL gait training. First, the patients were examined in a 10-meter walk test. To prevent the patient from falling, a walking aid such as cane, walker or suspension walker, was used depending on the patient's gait ability. Actually, 11 patients received 10-meter walk test with a walk aid and 10 patients did without a walk aid. Even in the patient who gain the gait ability, 10-meter walk test after HAL training was performed under the same conditions before HAL gait training, to eliminate the effect of use of walk aid. As the parameters of gait ability, gait velocity, step length, and cadence were measured during the middle 6 meters of the walk. After a sufficient seated rest (at least 5 minutes) following the 10-meter walk test, the patient underwent a 2-min walk test using a suspension walker without exception, during which the total gait distance was measured. Physical exertion was assessed using the modified Borg scale before and after the 2-min walk test.

Gait appearance

The modified Gait Abnormality Rating Scale (GARS-M)[16] was used to evaluate gait appearance. Patients undergoing a 10-meter walk test were recorded with a digital camera, and GARS-M was evaluated retrospectively. The GARS-M includes variables that describe a gait associated with an increased risk of falling. The GARS-M considers the following 7 items: 1) variability; 2) guardedness; 3) staggering; 4) foot contact; 5) hip range of motion (ROM); 6) shoulder extension, and arm-heel strike synchrony. Each item of the GARS-M is rated from 0 to 3, with a maximum of 21 points; a score of 21 points indicates the worst gate appearance.

Blood test

A blood sample was collected using a blood collection tube containing a serum separating agent, and centrifuged (3000 rpm, 4°C, 5 minutes) to obtain serum. Serum creatine phosphokinase (CPK), aspartate aminotransferase (AST), and lactic acid dehydrogenase (LDH) values were measured before HAL Treatment, mid-HAL Treatment (before the 5th HAL gait training

session), and after one full HAL Treatment series (after the 9th session) to assess iatrogenic muscle destruction caused by HAL gait training.

Muscle strength

A manual muscle testing (MMT) was used to evaluate muscle strength. MMT grade ranged from 0 to 5, with a grade of 0 representing no palpable or observable muscle contraction, 1 representing palpable or observable muscle contraction but no motion, 2 representing movement without gravity loading over the full ROM, 3 representing decreased movement against gravity over the full ROM, 4 representing movement against gravity and moderate resistance over the full ROM, and 5 representing movement against gravity and maximal resistance over the full ROM. The iliopsoas (IP), quadriceps femoris (QF), hamstrings (HM), tibial anterior (TA), and gastrocnemius (GC) muscles were tested.

ADL score

Functional Independence Measure (FIM) Score was recorded before and after HAL Treatment to evaluate the patient's disability in ADL.[17]

Statistical analysis

The data obtained from the 1st series of HAL Treatment and those from all patients were analyzed. The same analyses were also performed only for patients with neurological disease (ALS, SBMA, and CMT) and for those with myopathy (MD and IBM). The Wilcoxon signed-rank test was used to assess differences in gait velocity, step length, cadence, 2-minute walk distance, modified Borg Scale scores, total GARS-M Score, subscores of GARS-M, the MMT grade, the FIM Score before and after HAL Treatment. Change in serum CPK, AST, and LDH values was analyzed using the Friedman test followed by Tukey-Kramer multiple comparison test which was applied to detect significant differences between different serum enzymes related to skeletal muscle damage at the different time points of study. SPSS (version 23 for Macintosh; Chicago, IL, USA) was used and significance was $P<0.05$.

Results

All patients completed all HAL Treatment which as appropriate. Twenty-one patients underwent a total of 54 HAL Treatment series from April 2017 to October 2019. Five patients completed only 1 series, while 16 patients repeated several series of HAL Treatment (2 series in 8 patients, 3 series in 3 patients, 4 series in 1 patient, 5 series in 4 patients). One patient with SBMA complained of right hip pain during the 4th series of HAL Treatment, after which treatment was immediately stopped. No increase in serum CPK, AST or LDH was found, compared to those before HAL Treatment. The patient's right hip pain resolved without any medical treatment after 2 weeks, and the patient was able to complete the 5th HAL series after 3 months of 4th series. Given this interruption, data from this patient's 4th series were eliminated, and data from 53 series of 21 patients were consequently analyzed.

Gait ability

First HAL Treatment series

In comparison between before and after the 1st HAL Treatment series, step length on the 10-meter walk test significantly increased from 0.40±0.13 m/step to 0.45±0.13 m/step (P=0.015). Furthermore, the gait distance on the 2-minute walk test significantly increased from 70.7±43.7 m to 82.6±46.9 m (P<0.001). However, no significant changes were observed in gait velocity or cadence on the 10-meter walk test or in the modified Borg Scale after the 2-minute walk test. In the 14 patients with neurological disease, gait distance on the 2-minute walk test significantly increased from 64.8±47.8 m to 74.9±51.6 m from before to after the 1st HAL series. (P=0.016). In contrast, no significant changes in gait velocity, step length, cadence, or modified Borg Scale Score were found. In the 7 patients with myopathy, there was a significant improvement in their gait velocity from 0.83±0.30 m/s to 0.95±0.33 m/s (P=0.043), step length from 0.44±0.08 m/step to 0.50±0.11 m/step (P=0.039), and distance traveled on the 2-minute walk test from 82.3±34.3 m to 97.9±34.1 m (P=0.028) (Table II).

All HAL Treatment series

Analyzing all 53 HAL Treatment series in all patients, gait velocity improved significantly from 0.90±0.42 m/sec to 1.00±0.45 m/sec (P=0.001) and step length increased significantly from 0.44±0.12 m/step to 0.48±0.11 m/step (P=0.001) on the 10-meter walk test after HAL Treatment. In addition, gait distance on the 2-minute walk test significantly increased from 91.6±44.7 to 102.1±48.4 m (P=0.001). No significant changes in cadence on the 10-meter walk test or modified Borg scale score after the 2-minute walk test were observed. In patients with neurological disease, significant differences in gait velocity (from 0.81±0.45 m/sec to 0.91±0.49 m/sec; P=0.008) and step length (from 0.42±0.13 m/step to 0.46±0.12 m/step; P=0.005) on the 10-meter walk test from before to after treatment were observed. Furthermore, gait distance on the 2-minute walk test was significantly extended from 84.3±47.6 m before treatment to 94.0±53.0 m after treatment (P=0.004). No significant differences in cadence on the 10-meter walk test or in modified Borg Scale Score after the 2-minute walk test were observed. In patients with myopathy, significant improvements in gait velocity from 1.06±0.29 m/sec to 1.16±0.30 m/sec (P=0.012) and step length on the 10-meter walk test from 0.47±0.08 m/step to 0.51±0.09 m/step (P=0.011) were observed. Gait distance on the 2-minute walk test was also significantly extended from 104.4±36.7 m to 116.4±36.2 m (P=0.001). No significant changes in cadence on the 10-meter walk test or modified Borg scale score after the 2-min walk test were observed (Table III).

Gait appearance

Total GARS-M scores improved from before to after the 1st series of HAL Treatment from 11.1 ± 7.1 to 8.9 ± 7.5 (P=0.006). It is noteworthy that almost all subjects exhibited improved gait posture. After reviewing changes in each item of GARS-M with HAL Treatment, significant improvements in the variability (P=0.021), staggering (P=0.011), foot contact (P=0.01), and hip ROM (P=0.001) were noted. In patients with neurological disease, significant improvements in total GARS-M Score from 12.2±7.8 to 10.7±8.2 (P=0.022) and hip ROM subscore (P=0.012) were revealed. In patients with myopathy, significant improvements in total GARS-M Score from 8.8±5.1 to 5.2±4.6 (P=0.011) and subscore of foot contact (P=0.008) and hip ROM (P=0.046) were also revealed (Figure 2).

Blood tests

First HAL Treatment series

No significant differences in serum CPK, AST, or LDH levels between before treatment, mid-treatment (before the 5th HAL gait training session), and after the 1st series HAL Treatment were detected in all 21 patients. In 14 patients with neurological disease or 7 patients with myopathy, significant changes in serum CPK, AST, or LDH were also not detected (Figure 3). Comparison of serum values between mid-training and after training as performed using Tukey Kramer multiple comparisons test at baseline also showed no significant change.

All HAL Treatment series

No significant differences in serum CPK, AST, or LDH between the three-time points tested for all HAL Treatment series, including all patients, patients with neurological disease, or patients with myopathy, were detected (Figure 3). Comparison of serum values between mid-training and after training as performed using Tukey Kramer multiple comparisons test at baseline also showed no significant change.

Muscle strength

First HAL Treatment series

After the 1st series of HAL Treatment, the MMTs of the bilateral IP and TA were significantly increased. However, no significant changes in QF, HM, or GC were observed (Table IV). In all 21 patients, one MMT grade changes (either up or down) after the 1st series of HAL were noted. One grade MMT gains for the IPs of 5 patients, QF of 1 patient, HMs of 3 patients, TA of 6 patients, and GC of 2 patients, as well as one grade losses in the QF of 4 patients and the HM of 4 patients, were also noted.

All HAL Treatment series

After all HAL Treatment series, the MMTs for the bilateral IP, TA, and GC were significantly increased. However, no significant changes in QF or HM were noted (Table V). In all 53 series, changes in MMT grade after HAL Treatment were either one grade increases or decreases. One grade increase in MMT in the IP of 16 series, QF of 8 series, HM of 10 series, TA of 10 series, and GC of 8 series were also noted. One grade decreases also occurred in the IP of 4 series, QF of 5 series, HM of 6 series, and TA of 3 series.

ADL score

First HAL Treatment series

FIM score did not significantly change from 109.0±16.7 points before treatment to 109.2±17.1 points after treatment (P=0.63).

All HAL Treatment series

FIM score did not significantly change from 112.3±14.6 points before treatment to 112.4±14.8 points after treatment (P=0.98).

Complications

As mentioned above, 1 patient with SBMA complained of right hip pain during their 4th series of HAL Treatment. He was able to resume the 5th series after his pain decreased with rest. Another patient with IBM complained of left calf pain during the 3rd series of HAL Treatment. His calf pain gradually decreased with rest and he was able to complete the series on schedule.

Discussion

This study revealed that HAL gait training contributed to significant improvements in gait velocity, step length, and gait distance in both patients with neurological disease and those with myopathy. In contrast, there were no significant changes in serum CPK, AST, or LDH values during HAL gait training.

Wall *et al.*.[14] reported the systematic review with regard to clinical application of the HAL for gait rehabilitation, including 6 studies having only a HAL training group and 1 randomized clinical trial comparing a HAL training group with a conventional training group. Most of the patients were after stroke or spinal cord injury, and beneficial effects on improving several gait parameters and independence in gait were demonstrated. On the other hand, only 1 study involved 4 patients with NMD within a total of 38 patients, and 2 of them unfortunately worsened gait speed and cadence after 8 or 9 weeks of HAL gait training.[15] As the 1st test analyzing the efficacy and safety of the HAL gait training for gait ability, an investigator-initiated clinical trial was conducted in 24 patients with spinal muscular atrophy (SMA), SBMA, ALS, CMT, MD, distal myopathy, and congenital myopathy.[18] In this clinical trial, patients were randomly divided into 2 groups and cross-over testing was used to compare improvements in gait with conventional or HAL gait training. Gait distance improvement ratios on the 2-min walk test were calculated and revealed an additional effect of 10.066% (P=0.0369) with HAL gait training, with no critical complications interrupting HAL gait training. Based on these results, HAL was approved by the Pharmaceuticals and Medical Devices Agency in Japan as a medical device, and HAL gait training for the above-mentioned 8 NMDs was covered by public medical insurance in Japan.

In the present study, gait appearance also improved, shown by a significant change in GARS-M subscore for variability, staggering, foot contact, and hip ROM. This indicates that inconsistency and arrhythmicity in stepping and/or arm movements and body collapse towards the lateral side were reduced, standing phase was initiated by heel-strike rather than forefoot, and the hip joint ROM in the gait cycle increased.[16] In general, increased staggering causes of greater energy consumption and slower gait velocity.[19] The heel rocker was one of the functions of storing the driving force of kinetic energy during gait, and the driving force contributes to the increase of gait velocity. In this study, increased gait velocity might reflect improvement in staggering and foot contact after HAL training. There were 7 factors that determine the step length: increased ankle dorsiflexion angle, heel separation, increased hip extension angle, posterior pelvic rotation in terminal stance phase, and increased hip flexion angle, mild knee flexion, anterior pelvic line in terminal swing phase.[20] It was suggested that increased hip joint ROM might contribute to extended step length after HAL gait training in this study.

Bennett *et al.*[21] proposed the concept of overwork weakness, a phenomenon in which muscular strength decreased with excessive muscle strengthening exercise for the treatment of peripheral neuropathies such as post-polio or Guillain-Barré syndromes. Muscle fibers in NMD are

abnormally vulnerable to contraction-induced injury due to the absence, or lack, of mechanical reinforcement of the sarcolemmal membrane.[22] From the view of overwork weakness, the safety of exercise training has still been controversial issue for patients with NMD, because of a lack of good controlled studies due to the rarity of disease.[23] Patients with overwork weakness often complain of muscle pain, muscle weakness, and their laboratory studies indicate elevated serum CPK value.[24] Increased serum CPK has also been noted after training of stairs and bicycles in patients with muscular dystrophy.[25] Furthermore, Dalakas *et al.*[26] found, in muscle biopsied from a polio-paralyzed but partially recovered area in patients with overwork weakness, mixed neurogenic and myogenic changes it could cause increased serum CPK. In this way, serum CPK value is a useful indicator to determine exercise intensity in patients with NMD.[27]

Although the high evidenced-based rehabilitation protocol has not been established, the clinicians and therapists prefer to more mild and less invasive exercise for weakened muscle. Mori *et al.*[28] recommended the stretching, proprioceptive exercise and treadmill training, which had an objective benefit on patients affected by neurological disease without causing overwork weakness. Since HAL gait training in the present study was performed in an over-ground style, we were seriously concerned about a risk of exercise-induced muscle injury. HAL Treatment was repeated over a total of 53 series in 21 patients, and those were fortunately completed without a significant increase in serum CPK values or a significant down-grading of MMT. Only 1 patient with IBM and 1 with SBMA complained of hemilateral calf and hip pain, respectively. The pain in both patients relieved within a few weeks without any specific treatments. Motion assist by HAL power units placed on the hip and knee joint, which synchronizes with hip and knee muscle activities, might avoid excessive workload of the muscles and their injuries in most of patients. Based on these findings, it seems that no significant muscle damage was caused by HAL gait training, which may be safely used to treat NMDs without inducing overwork weakness.

Limitations of this study

Despite its benefits, some limitations of the current study should be acknowledged. First, a lack of control group made impossible to compare the effects on gait ability between conventional rehabilitation and rehabilitation with HAL programs. Therefore, the pure effect of HAL gait training has been unclear, and it is a major limitation of this study. Second, the patients were recruited from different disease and patients' clinical presentations were heterogeneous with regard to the subtype, stage or severity of disease. In addition, the number of patients in each disease was too small and not enough to statistically analyze the difference in outcomes of HAL gait training. Furthermore, one series of gait rehabilitation consisted of 9 HAL training, with a varied interval of 1 to 9 months between series. Given this, the positive and negative effects of continuous HAL gait training remain unclear. Finally, muscle strength was assessed only with MMT, and a subclinical decrease in muscle strength could therefore not be detected. Nevertheless, the present study provides the first insights into the adverse effects of robotic gait rehabilitation on serum CPK values in patients with NMD. Further studies would need to enlarge the population size, adding a control group of patients receiving conventional rehabilitation only.

Conclusions

Although this study conducted the HAL gait training under only the limited practical protocol, it was demonstrated that HAL gait training might be used to improve gait ability in patients with

progressive NMD. Furthermore, HAL gait training does not lead to overwork weakness or increased levels of serum enzymes related to skeletal muscle damage, when utilized with an appropriate intensity and frequency. On the other hand, no significant change in FIM score after HAL gait training suggested that the statistically significant but small change in several gait parameters obtained under the best walking environments during walk tests is not sufficient to improve the patient's level of disability in daily life.

References

1. NDB open data [Internet]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html [cited 2021, Jun 9].
2. Majmudar S, Wu J, Paganoni S. Rehabilitation in amyotrophic lateral sclerosis: why it matters. Muscle Nerve 2014;50:4–13. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=24510737&dopt=Abstract https://doi.org/10.1002/mus.24202
3. Cup EH, Pieterse AJ, Ten Broek-Pastoor JM, Munneke M, van Engelen BG, Hendricks HT, *et al.* Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil 2007;88:1452–64. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=17964887&dopt=Abstract https://doi.org/10.1016/j.apmr.2007.07.024
4. Voet NB, van der Kooi EL, Riphagen II, Lindeman E, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev 2010;1:CD003907. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=20091552&dopt=Abstract https://doi.org/10.1002/14651858.CD003907.pub3
5. Colombo G, Joerg M, Schreier R, Dietz V. Treadmill training of paraplegic patients using a robotic orthosis. J Rehabil Res Dev 2000;37:693–700. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11321005&dopt=Abstract
6. Veneman JF, Kruidhof R, Hekman EE, Ekkelenkamp R, Van Asseldonk EH, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. IEEE Trans Neural Syst Rehabil Eng 2007;15:379–86. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=17894270&dopt=Abstract https://doi.org/10.1109/TNSRE.2007.903919
7. Yang A, Asselin P, Knezevic S, Kornfeld S, Spungen AM. Assessment of In-Hospital Walking Velocity and Level of Assistance in a Powered Exoskeleton in Persons with Spinal Cord Injury. Top Spinal Cord Inj Rehabil 2015;21:100–9. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=26364279&dopt=Abstract https://doi.org/10.1310/sci2102-100
8. Tefertiller C, Hays K, Jones J, Jayaraman A, Hartigan C, Bushnik T, *et al.* Initial Outcomes from a Multicenter Study Utilizing the Indego Powered Exoskeleton in Spinal Cord Injury. Top Spinal Cord Inj Rehabil 2018;24:78–85.

https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=29434463&dopt=Abstract https://doi.org/10.1310/sci17-00014

9. Nam KY, Kim HJ, Kwon BS, Park JW, Lee HJ, Yoo A. Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. J Neuroeng Rehabil 2017;14:24. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=28330471&dopt=Abstract https://doi.org/10.1186/s12984-017-0232-3
10. Quintero HA, Farris RJ, Hartigan C, Clesson I, Goldfarb M. A Powered Lower Limb Orthosis for Providing Legged Mobility in Paraplegic Individuals. Top Spinal Cord Inj Rehabil 2011;17:25–33. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=22707874&dopt=Abstract https://doi.org/10.1310/sci1701-25
11. Kawamoto H, Taal S, Niniss H, Hayashi T, Kamibayashi K, Eguchi K, *et al.* Voluntary motion support control of Robot Suit HAL triggered by bioelectrical signal for hemiplegia. Annu Int Conf IEEE Eng Med Biol Soc 2010;2010:462–6. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=21095652&dopt=Abstract https://doi.org/10.1109/IEMBS.2010.5626191
12. Suzuki K, Mito G, Kawamoto H. Intention-based walking support for paraplegia patients with Robot Suit HAL. Adv Robot 2007;21:1441–69. https://doi.org/10.1163/156855307781746061
13. Saita K, Morishita T, Arima H, Hyakutake K, Ogata T, Yagi K, *et al.* Biofeedback effect of hybrid assistive limb in stroke rehabilitation: A proof of concept study using functional near infrared spectroscopy. PLoS One 2018;13:e0191361. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=29338060&dopt=Abstract https://doi.org/10.1371/journal.pone.0191361
14. Wall A, Borg J, Palmcrantz S. Clinical application of the Hybrid Assistive Limb (HAL) for gait training-a systematic review. Front Syst Neurosci 2015;9:48. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=25859191&dopt=Abstract https://doi.org/10.3389/fnsys.2015.00048
15. Kubota S, Nakata Y, Eguchi K, Kawamoto H, Kamibayashi K, Sakane M, *et al.* Feasibility of rehabilitation training with a newly developed wearable robot for patients with limited mobility. Arch Phys Med Rehabil 2013;94:1080–7. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=23313372&dopt=Abstract https://doi.org/10.1016/j.apmr.2012.12.020
16. VanSwearingen JM, Paschal KA, Bonino P, Yang JF. The modified Gait Abnormality Rating Scale for recognizing the risk of recurrent falls in community-dwelling elderly adults. Phys Ther 1996;76:994–1002.

https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8790277&dopt=Abstract https://doi.org/10.1093/ptj/76.9.994

17. Iuppariello L, Nespoli M, Iammarone F, Bertella M, Riccio I, Cardillo M, *et al.* The evaluation of the joint quasi-stiffness during the robot-assisted gait training: a pilot study. IFMBE Proc •••;76:634–9. https://doi.org/10.1007/978-3-030-31635-8_76
18. HAL for Medical Use (Lower Limb Type) Summary: edition 1 (Japanese) [Internet]. Available from: https://www.cyberdyne.jp/products/pdf/HT010910A-U01_R1.pdf [cited 2021, Jun 9].
19. Perry J, Burnfield JM. Gait analysis. Normal and Pathological Function Second Edition. USA: SLACK incorporated; 2010. p. 182-4.
20. Kirsten G. Observational gait analysis. Downey, CA: Rancho Los Amigos National Rehabilitation Center; 2003. p.8-9.
21. Bennett RL, Knowlton GC. Overwork weakness in partially denervated skeletal muscle. Clin Orthop 1958;12:22–9. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13619074&dopt=Abstract
22. Voet NB. Exercise in neuromuscular disorders: a promising intervention. Acta Myol 2019;38:207–14. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=31970319&dopt=Abstract
23. Abresch RT, Han JJ, Carter GT. Rehabilitation management of neuromuscular disease: the role of exercise training. J Clin Neuromuscul Dis 2009;11:7–21. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=19730017&dopt=Abstract https://doi.org/10.1097/CND.0b013e3181a8d36b
24. Hachisuka K, Ogata H, Ide M. [Overuse Muscle Weakness in Post-polio Patients]. Sogo Rehabilitation 1988;16:513–5. [Japanese.]
25. Yamaji K, Nakane K. Change in serum CPK value and physical therapy for myotonic dystrophy. Seikeigeka MOOK 1978;2:111–21. [Japanese.]
26. Dalakas MC. Morphologic changes in the muscles of patients with postpoliomyelitis neuromuscular symptoms. Neurology 1988;38:99–104. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3336469&dopt=Abstract https://doi.org/10.1212/WNL.38.1.99
27. Peach PE. Overwork weakness with evidence of muscle damage in a patient with residual paralysis from polio. Arch Phys Med Rehabil 1990;71:248–50. https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2317146&dopt=Abstract
28. Mori B, Norman K, Brooks D, Herold J, Beaton DE. Development of the Canadian Physiotherapy Assessment of Clinical Performance: a new tool to assess physiotherapy students' performance in clinical education. Physiother Can 2015;67:281–9

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Masakazu Kogawa participated in the design and coordination of the study, data collection, data analyses and drafted the manuscript;Kazutomo Miura participated in the design of the study, and patients' enrollment. Kazuhiro Yasuda and Hiroaki Ishiyama were involved with the date collection and proceeding;Yasuyuki Ishibashi helped to organize the study and assisted with the review of the manuscript. Eiichi Tsuda supervised through the whole study process and review the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements.—We are very grateful to all the patients and family members who kindly agreed to participate in this study, and to the physical therapists at the Hirosaki University Hospital Department of Rehabilitation for their technical support with data collection. Furthermore, we would like to thank Editage (www.editage.jp) for English language editing.

History.—Article first published online:_____. - Manuscript accepted: May 31, 2021. - Manuscript revised: January 14, 2021. - Manuscript received: May 18, 2020.

Figure 1.—HAL gait training apparatus and set-up.

Figure 2.—The modified Gait Abnormality Rating Scale (GARS-M) subscores before and after HAL gait training.

Figure 3.—Serum creatine phosphokinase (CPK), aspartate aminotransferase (AST), and lactic acid dehydrogenase (LDH) values before, mid, and after HAL gait training.

Table 1. Patient characteristics.

Case No.	Age (y)	Sex	Diagnosis	Disease duration (y)	Ambulation	Assistive Device	HAL gait training series
1	56	M	ALS	7	Independently	None	2
2	67	M	ALS	8	Supervision	suspension walker	1
3	75	M	ALS	10	Independently	None	5
4	84	M	ALS	1	Supervision	T-cane	2
5	78	M	ALS	2	Supervision	suspension walker	1
6	74	M	ALS	1	Supervision	Walker	2
7	61	F	ALS	0.5	Supervision	Walker	2
8	58	F	ALS	7	Supervision	suspension walker	5
9	61	F	ALS	0.5	Independently	None	2
10	54	F	ALS	4	Supervision	suspension walker	2
11	48	F	ALS	2	Independently	None	1
12	39	M	MD	19	Independently	None	4
13	39	M	MD	13	Independently	None	3
14	67	M	MD	10	Independently	None	5
15	47	F	MD	2	Supervision	Walker	2
16	54	F	MD	9	Independently	T-cane	2
17	56	M	SBMA	24	Independently	None	5
18	63	M	SBMA	0.5	Independently	None	3
19	72	M	IBM	14	Independently	T-cane	2
20	69	M	IBM	3	Independently	T-cane	1
21	53	F	CMT	17	Independently	None	1

Abbreviations: M, male; F, female; ALS, amyotrophic lateral sclerosis; MD, myotonic dystrophy; SBMA, spinal and bulbar muscular atrophy; IBM, inclusion body myositis; CMT, Charcot -Marie -Tooth disease

Table II.—Results of walk tests in the 1st HAL gait training series.

	All patients			Neurological disease patients			Myopathy patients		
	Before HAL	After HAL	P value	Before HAL	After HAL	p-value	Before HAL	After HAL	P value
10-m walk test									
Velocity (m/s)	0.74±0.43	0.79±0.43	0.23	0.68±0.49	0.71±0.46	0.81	0.83±0.30	0.95±0.33	0.043*
Step length (m/step)	0.41±0.14	0.45±0.13	0.031*	0.38±0.16	0.42±0.13	0.14	0.44±0.08	0.50±0.11	0.039*
Cadence (step/s)	1.61±0.75	1.69±0.64	0.37	1.48±0.84	1.59±0.74	0.34	1.88±0.47	1.88±0.37	0.86
2-min walk test									
Distance (m)	71.9±43.9	81.8±46.9	0.004*	64.8±47.8	74.9±51.6	0.016*	82.3±34.3	97.9±34.1	0.028*
Borg Scale Score	4.6±2.4	4.3±2.8	0.59	5.1±2.2	5.0±2.5	0.83	3.8±2.9	3.0±3.2	0.49

*Significant difference ($P<0.05$) with HAL treatment.

Table III.—Results of walk tests in all HAL gait training series.

	Before HAL	After HAL	P value	Before HAL	After HAL	P value	Before HAL	After HAL	P value
10-m walk test									
Velocity (m/s)	0.90±0.42	1.00±0.44	0.001*	0.81±0.45	0.91±0.49	0.008*	1.06±0.29	1.16±0.30	0.012*
Step length (m/step)	0.44±0.12	0.48±0.11	0.001*	0.42±0.13	0.46±0.12	0.014*	0.47±0.08	0.51±0.09	0.011*
Cadence (step/s)	1.82±0.67	1.89±0.62	0.083	1.72±0.76	1.80±0.70	0.18	2.02±0.41	2.06±0.40	0.22
2-min walk test									
Distance (m)	91.6±44.7	102.1±48.4	0.001*	84.3±47.6	94.0±53.0	0.004*	104.4±36.7	116.4±36.2	0.001*
Borg scale score	4.5±2.4	4.2±2.8	0.23	4.8±1.9	4.7±2.5	0.86	4.2±3.1	3.3±3.0	0.063

*Significant difference ($P<0.05$) with HAL treatment.

Table IV—Results of MMT in the 1st HAL gait training series.

Rt. iliopsoas				Lt. iliopsoas			
MMT	Before	After	P value	MMT	Before	After	P value
5	6	9	0.021	5	6	8	0.021
4	6	3		4	6	5	
3	4	6		3	3	4	
2	5	3		2	6	4	
1	0	0		1	0	0	
0	0	0		0	0	0	
Rt. quadriceps femoris				Lt. quadriceps femoris			
MMT	Before	After	P value	MMT	Before	After	P value
5	9	8	0.18	5	9	8	0.32
4	4	5		4	4	4	
3	4	2		3	4	5	
2	4	6		2	4	4	
1	0	0		1	0	0	
0	0	0		0	0	0	
Rt. hamstrings				Lt. hamstrings			
MMT	Before	After	P value	MMT	Before	After	P value
5	2	2	0.66	5	2	2	1
4	7	7		4	8	7	
3	8	7		3	4	6	
2	4	5		2	7	6	
1	0	0		1	0	0	
0	0	0		0	0	0	

Rt. tibialis anterior				Lt. tibialis anterior			
MMT	Before	After	P value	MMT	Before	After	P value
5	3	4	0.015	5	2	4	0.01
4	4	6		4	4	4	
3	4	3		3	5	4	
2	6	4		2	5	4	
1	3	4		1	3	4	
0	1	0		0	2	1	
Rt. gastrocnemius				Lt. gastrocnemius			
MMT	Before	After	P value	MMT	Before	After	P value
5	2	2	0.16	5	2	2	0.32
4	0	1		4	1	2	
3	4	4		3	3	2	
2	14	13		2	14	14	
1	0	0		1	0	0	
0	0	0		0	1	1	

Table V.—Results of MMT in all HAL gait training series.

Rt. iliopsoas				Lt. iliopsoas			
MMT	Before	After	P value	MMT	Before	After	P value
5	15	20	0.006	5	16	19	0.0036
4	17	17		4	21	21	
3	14	10		3	7	6	
2	7	6		2	9	7	
1	0	0		1	0	0	
0	0	0		0	0	0	
Rt. quadriceps femoris				Lt. quadriceps femoris			
MMT	Before	After	P value	MMT	Before	After	P value
5	19	20	1	5	19	23	0.709
4	17	17		4	18	13	
3	6	3		3	6	5	
2	11	13		2	8	10	
1	0	0		1	2	2	
0	0	0		0	0	0	
Rt. hamstrings				Lt. hamstrings			
MMT	Before	After	P value	MMT	Before	After	P value
5	5	5	1	5	4	4	0.159
4	18	18		4	20	21	
3	17	17		3	17	17	
2	13	13		2	12	11	
1	0	0		1	0	0	
0	0	0		0	0	0	

Rt. tibialis anterior				Lt. tibialis anterior			
MMT	Before	After	P value	MMT	Before	After	P value
5	11	13	0.012	5	10	14	0.023
4	17	18		4	20	16	
3	7	5		3	6	7	
2	14	13		2	9	8	
1	4	4		1	7	7	
0	0	0		0	1	1	
Rt. gastrocnemius				Lt. gastrocnemius			
MMT	Before	After	P value	MMT	Before	After	P value
5	2	3	0.012	5	2	2	0.023
4	4	5		4	6	10	
3	13	14		3	11	8	
2	34	31		2	33	32	
1	0	0		1	0	0	
0	0	0		0	1	1	

Figure 1.

Figure 2.

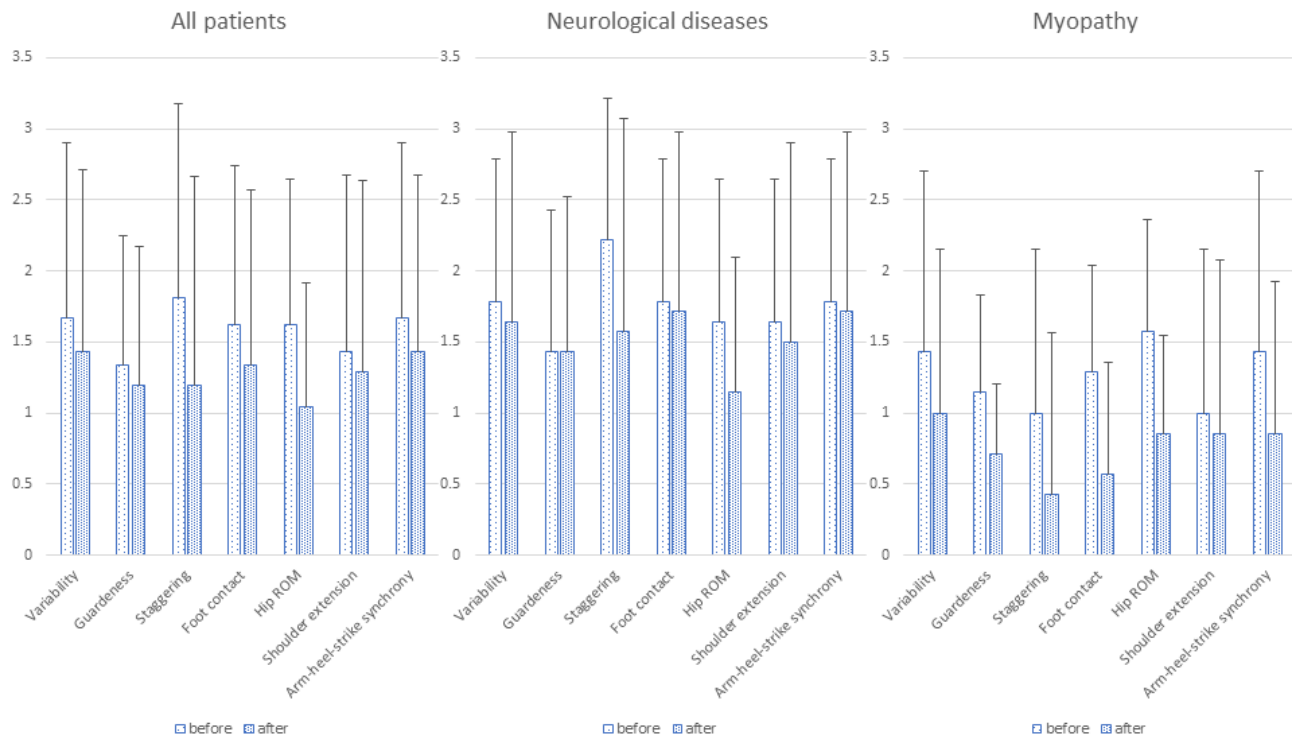
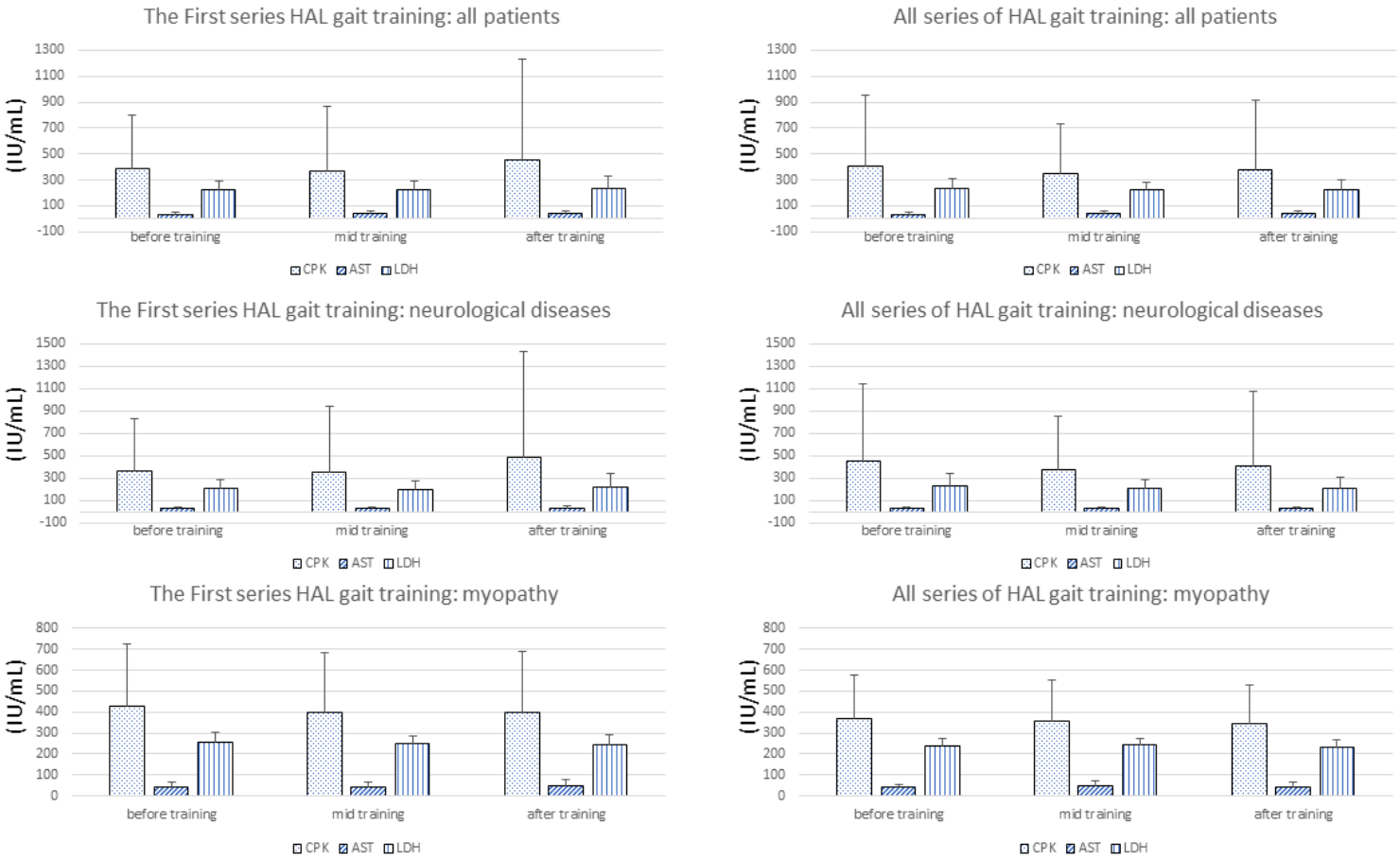

All patients
Neurological diseases
Myopathy
3.5
3
2.5
2
1.5
1
0.5
0
Variability
Guardeness
Staggering
Foot contact
Hip ROM
Shoulder extension
Arm-heel-strike synchrony
before
after

Figure 3.


The First series HAL gait training: all patients
All series of HAL gait training: all patients
The First series HAL gait training: neurological diseases
All series of HAL gait training: neurological diseases
The First series HAL gait training: myopathy
All series of HAL gait training: myopathy
(IU/mL)
before training
mid training
after training
CPK
AST
LDH