Strength Training in Patients With Myotonic Dystrophy and Hereditary Motor and Sensory Neuropathy: A Randomized Clinical Trial

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ABSTRACT. Lindeman E, Leffers P, Spaans F, Drukker J, Reulen J, Kerckhoffs M, Köke A. Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: a randomized clinical trial. Arch Phys Med Rehabil 1995;76:612-20.

• A randomized clinical trial on the effects of strength training was performed in myotonic dystrophy (MyD) patients and patients with hereditary motor and sensory neuropathy (HMSN). Training and most measurement tools involved the proximal lower extremity muscles. The participants trained 3 times a week for 24 weeks with weights adapted to their force. Strength was evaluated by isokinetically measured knee torque. Fatiguability was assessed by the time an isometric contraction could be sustained. Functional performance was measured by timed motor performance and by questionnaires on functional performance. Serum myoglobin (Mb) levels were determined to detect changes in muscle fiber membrane permeability. The MyD group included 33 participants, and the HMSN group included 29 participants. Within each diagnostic group, patients were individually matched and subsequently randomized for treatment allocation. In the MyD patients, none of the measurement techniques showed any training effect. Neither were there signs of deterioration caused by the training. In the HMSN group, knee torques increased. Timed motor performance did not change, although the questionnaires showed an improvement on items related to upper-leg function. Mb levels did not change significantly as a result of the training. In conclusion, the MyD group showed neither positive nor negative effects of the training protocol, whereas the training produced a moderate increase in strength and leg-related functional performance in the HMSN group.

In inherited neuromuscular disorders, weakness is considered to be the main problem. Strength training may be of help in counteracting a loss of muscular function. A few reviews on strength training in patients with neuromuscular disorders have been published.[1-3] Most studies concerned Duchenne muscular dystrophy (DMD) or a variety of neuromuscular diseases, with DMD usually the largest group.[4-7] Recently, several studies have been published about strength training in adults with slowly progressive neuromuscular disorders.[8-12] Results suggest that many patients benefited from the exercises. All of these studies however, have substantial methodologic shortcomings, such as too few patients, a large variety of disorders,[8-13] or a combination of strength training and other therapeutic interventions.[9,14] The main shortcoming of all studies, however, is the absence of a separate nonexercising control group having the same disorder. Three studies used the opposite extremity as a control,[9-11] which must be considered inappropriate because of possible cross-over training effects.[15] In one study, training effects in neuromuscular patients were compared with these effects in healthy subjects.[13] Changes in functionality were not evaluated in the studies on strength training. It is believed that further studies are needed to resolve whether strength training is useful in patients with slowly progressive neuromuscular disorders.

The purpose of this study was to determine whether short-term muscle strength training is efficacious for improving impairments (loss of strength and increased fatiguability), disabilities (decrease of functional abilities and actual functional performance), and handicap (measured as "well-being"). This first clinical trial was done with patients with the most common hereditary neuromuscular disorders of adulthood: myotonic dystrophy (MyD, Curschmann-Steinert disease) and hereditary motor and sensory neuropathy (HMSN, Charcot-Marie-Tooth disease).[16]

MATERIALS AND METHODS

Patients

Patients diagnosed with MyD or HMSN (types I or II) on the basis of their clinical picture, electromyography and nerve conduction studies were invited to participate in this trial. They had to live within 100km distance from Maastricht and be between 16 and 60 years of age. They were informed about the trial by their neurologist, physiatrist, and/or the Dutch association for neuromuscular diseases (*Vereniging Spierziekten Nederland*). They were invited to the authors' department to familiarize themselves with the measurements to be performed during the study.

Subjects were excluded if there were contraindications for muscle strengthening exercises or if they had other disabling

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disorders that might influence the scoring in the functional tests. They also had to be prepared and motivated to visit all measurements sessions, to train (if allocated to the training group), and to refrain from training (if allocated to the control group). Patients were informed about the importance of good compliance and about the validity implications for the study of "loss to follow-up."

A qualification period[17] was included to accomplish the following: determine the suitability of patients for the trial; give optimal information before patients signed the informed consent; and obtain matching data. To optimize compliance, the patients were also informed about the consequences for the interpretation of the outcome of the trial if they did not follow instructions. The pilot measurements also allowed the observers to gain experience with the measurement protocol. Medical history was obtained from all patients. Because cardiac abnormalities are frequent in MyD,[18-21] an electrocardiogram (ECG) was taken and assessed in all MyD patients who had not been recently examined by a cardiologist.

Proximal lower extremity muscles were chosen for training and strength measurements because of their impact on daily life functioning and because of their relation with functional performance.[22,23] Within both diagnostic groups, patients were individually matched as closely as possible on muscle strength (knee extension torque divided by body weight = peak/body weight ratio) and on performance in a stair-climbing test. Matching was done because it is reasonable to presume that these are predictive of trainability of muscle strength and functional ability.[3,8] Within each matched pair, patients were randomly assigned to the training or control group.

Exercises

Patients were instructed by a physical therapist on how to perform the exercises at home. Knee extension and flexion exercises and hip extension and abduction exercises were performed with weights. The weight was varied by placing lead in bandages. These bandages were fixed to the limb or trunk with velcro. The subjects trained at home, three times a week, for 24 weeks. Before the study period and every second week thereafter the physical therapist visited the patient to adjust the weights to the actual muscle strength.[24-26] Muscle strength was estimated by the therapist by assessing one repetitive maximum (1RM)[27] for the relevant concentric movement.

During the first 8 weeks, training was performed at 60% of 1RM. Contractions were repeated 25 times, three series in a row, with a 1-minute rest in between. In the second 8-week period, the three series were performed with weights of 70% of 1RM, 15 times, and during the last period with 80% of 1RM, 10 times. All exercises could be executed within 30 minutes. If there were muscle complaints, training weights were adapted and instructions were given for muscle stretching exercises.

In order to optimize and check compliance, a training diary was to be completed. At every visit the therapists noted their impression about compliance and the quality of performance of the exercises.

Measurements

Outcome measurements were performed at the start of the study period (t0) and after 8 (t8), 16 (t16), and 24 (t24) weeks of follow-up. For each individual participant, all measurements were taken at the same day of the week, at the same time of the day, and by the same observer. Observers of the outcome measurements were blinded for treatment allocation. The participants were blinded for earlier results, except for the visual analogue scale (VAS) questionnaire data. In order to obtain an impression about the effectiveness of blinding, observers scored their degree of certainty about the patient being a member of the training group on a VAS at t24.

Muscle strength was measured isokinetically as maximum concentric knee torques at 120, 60, and 30° per second, and isometrically as maximum voluntary contraction (MVC). Endurance was measured as maximum duration of contraction at 80% of MVC. All these measurements were performed on a CYBEX II isokinetic dynamometer.[a] This was chosen because strength measurements on a dynamometer, especially of isokinetic and isometric knee torques, are reproducible[22,28-30] and give a better differentiation of strength than manual muscle testing.[31-33] Damp setting was 2. Data were analyzed on a Cybex data reduction computer. Subjects were instructed to extend and flex the knee as forcefully and as fast as possible three times in a row. The highest peak torque value of these three movements was used in further calculations. Subjects started with three practice movements at each velocity. Rather low velocities were chosen because persons with reduced strength cannot achieve high velocities.[22] MVC and endurance tests were performed at a knee angle of 60° from full extension. For the sake of comparability, the endurance test had to be performed at the same torque value (80% of MVC at t0) during the follow-up measurements.

Functional performance was measured with two techniques:

1. Actual functional abilities were measured by time scored activities,[34,35] which were performed as fast as possible: ascending and descending stairs, rising from a chair, rising from supine on a physical exercise table and walking 50m; walking 6m was performed at natural speed. All these activities take significantly more time in these patients than in healthy subjects.[36] The use of aids while performing the activities was kept equal over the four measurement sessions.
2. Questionnaires about disease-related difficulties in performing daily life activities.[37] Questionnaires were a modification of the functional part of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC).[38] They were scored on a VAS, with "no difficulty" on the left end and "extreme difficulty" on the right end. Moreover, at t0 all subjects were asked to identify the disease-related problems they faced in daily life. The questionnaire was adapted from the Problem Elicitation Technique (PET).[39] Participants were asked to list activities that gave the greatest difficulties in their own life. These activities were clustered

in groups. Physical and social functions were distinguished. Only for the physical functions were the patients asked whether they believed the problem was caused by disturbances of leg, arm, back, or other functions. Those activities related to leg function that a person stated to be the most important were evaluated separately over the trial period. Each item mentioned was evaluated on a VAS at every measurement session. (Questionnaires are available on request from the first author.)

In order to be able to assess comparability with other study groups[40,41] the Sickness Impact Profile (SIP) was measured once.

In order to detect a possible harmful effect of exercise on the muscle fiber membrane, the permeability of the membrane was assessed by measuring serum myoglobin (Mb) levels just before and 1 hour after a test session.[42] Mb levels were determined with a radioimmunoassay.[b]

Statistical Analysis

Knee torques at all three velocities of both legs in each measurement session were averaged for further calculation because of the very strong correlations between the changes at the different velocities.

The differences between training and control subjects were calculated over the three training periods (changes between t0 and t8, t0 and t16, and between t0 and t24). Differences were compared using paired *t* tests and two sample *t* tests (to look for differences because of the small number of complete pairs). Only results of the paired *t* tests at t0 and t24 will be presented because they showed the most relevant differences between the groups. In order to consider the trend over the outcome measurements at t8, t16, and t24, the differences in knee extension torques over the four measurements within each pair were calculated. This trend was evaluated with the Page test for ordered alternatives.[43]

Blinding of the observers was evaluated by calculation of the potential agreement beyond chance, as reflected by kappa.

RESULTS

Group Composition

In the qualification period 11 participants withdrew or were excluded from further participation because they met the exclusion criteria (table 1): (a combination of) motivational problems ($n = 5$), other disorders that influence scoring on the functional tests such as pain ($n = 2$), herniated lumbar disc with drop-foot ($n = 1$), overweight ($n = 1$), and osteomyelitis ($n = 1$). One HMSN patient had neither type I nor II. Some patients were excluded because of contraindications for muscle strength exercises: 3 had diabetes mellitus; 1 MyD and 1 HMSN patient were excluded because of coronary heart disease. No MyD patient was excluded because of ECG abnormalities. Four patients who had already been randomized withdrew before disclosure of the treatment allocation: 2 because of medical problems; 2 because of social problems.

Of the 33 MyD subjects who ultimately started the trial, 2 had the congenital form; the others had the classical, adult type. In the HMSN group, 21 subjects had type I and 6 had type II, whereas the type was unknown in 2.

Table 1: Numbers of Subjects and Matched Pairs During the Various Stages of the Study

	MyD Subjects	MyD Matched Pairs	HMSN Subjects	HMSN Matched Pairs
Pilot	43		34	
Excluded	7		4	
Randomized	36	18	30	15
Dropped out before disclosure of allocation	3		1	
At 0 weeks (t0)	33	15	29	14
At 8 weeks (t8)	33	15	29	14
At 16 weeks (t16)	33	15	29	14
Dropped out	1		1	
At 24 weeks (t24)	32	14	28	13

All patients were ambulatory. Six MyD and 7 HMSN patients used ankle foot orthoses; of these patients in each diagnostic group, 1 patient used crutches and 2 MyD patients used a cane.

One MyD (training group) patient and 1 HMSN (control group) patient were unable to participate in the final test session because of knee problems. However, they did fill in the follow-up questionnaires.

Baseline data of the training and control groups that may be relevant for prognostic comparability are presented in table 2. Knee torque measurements per subject have been averaged over both legs and all three speeds.

Functional and psychosocial scores of the SIP at t0 were calculated. These scores were higher for the MyD group (mean 13.7% and 10.5%, respectively) than the corresponding scores of the HMSN group (mean 10.1% and 5.6%, respectively).

Training Report

No serious side effects of the training occurred. Training loads could be gradually increased in all patients, because RM improved. Three rather weak MyD patients were unable to perform the exercises entirely according to the training instructions. Three MyD patients and one HMSN patient took their training at a fitness center during the third training period because it was not possible to put enough lead in their bandages. One MyD patient stopped training during the second training period on the advice of his general practitioner because of back complaints. This patient also failed to attend the last test session because of knee problems. One HMSN patient stopped training during the third period because of social problems. This patient completed all the test sessions. Complaints owing to overuse appeared mainly at the start of a new training period.

Blinding

At t24, the observers misclassified 10 patients from each diagnostic group with regard to treatment allocation. In MyD this misclassification concerned 36% of the patients in the training group and 28% in the control group. Of the misclassified HMSN patients, 43% were in the training group and

Table 2: Base-Line Data for the Control and the Training Groups. (Means and SD)

	Myotonic Dystrophy		HMSN	
	Controls	Training	Controls	Training
Number of patients	15	15	14	14
Sex (male)	12 (80%)	9 (60%)	7 (50%)	6 (43%)
Age	37 (10)	40 (11)	38 (11)	35 (10)
range (years)	20-55	18-57	17-57	16-50
Knee torque extension (Nm)	60 (32)	70 (37)	101 (28)	91 (31)
Knee torque flexion (Nm)	25 (16)	37 (19)	42 (18)	41 (16)
PBWR extension (Nm/kg)	94 (47)	99 (53)	142 (23)	138 (36)
PBWR flexion (Nm/kg)	39 (23)	52 (26)	60 (20)	63 (23)
Up and down stairs (sec)	33 (18)	47 (44)	22 (6)	23 (6)

NOTE. PBWR extension and walking up and down stairs were matching variables.

28% in the control group. Of the correctly classified patients, the observers knew the group allocation in 28% of the MyD patients in the training group, 11% of the MyD controls, 28% of the HMSN training group, and 14% of the HMSN controls because the patients had provided this information.

After selection of the patients with maintained blinding, kappa was calculated between the real group allocation and the opinion of the observer. Kappa was 19% for the MyD subjects and 7% for the HMSN subjects. This means that the agreement is very low and might be caused by chance.

Strength

Knee torques of the MyD group did not show any statistically significant difference between the training and control groups, neither with the two-sample t test nor with a paired t test between the intact matched pairs (table 3). Neither did the Page test for ordered alternatives reveal any statistically significant trend on differences over the 4 measurement sessions. Figure 1 shows that even the weaker subjects showed no signs of overwork weakness, as no strength decrease was found. The 4 persons with the lowest torques showed no training effect; these were also the patients who were unable to optimally perform the exercises. The other 14 patients showed a small, but statistically nonsignificant, change.

In the HMSN group a moderate training effect was found (table 3, fig 2): isokinetic extension torques increased by 14% (Page test: $p < 0.005$), flexion torques by 13%. Only at the measurement after 8 weeks did one MyD patient and two HMSN patients in the training group have muscle soreness and a transient strength reduction. Endurance did not change significantly in either group. No difference in trainability was observed between men and women.

Functional Abilities

Results of the time scored activities of both patient groups did not change significantly, except for an improvement on "walking 6m at natural speed" in the HMSN group. From the questionnaires based on the WOMAC it appeared that both training groups experienced improvement of specific activities. In MyD these changes were statistically significant for questions on standing, getting into and out of a car, and putting on socks. In the HMSN group statistically significant changes were reported on ascending stairs, rising from sitting, getting into and out of a car, putting on socks, and lying down on the bed.

Changes in knee torques were not related to changes in timed motor performance or changes on the questionnaire items (data not shown).

Most of the hindrance reported on the PET questionnaires

Table 3: Mean Change (SD in Brackets) Between t0 and t24, as found with a Paired t Test

	Myotonic Dystrophy			HMSN		
	Control (n = 14)	Training (n = 14)	P	Control (n = 13)	Training (n = 13)	P
Isokinetic knee torque extension (Nm)	1.4 (8.2)	5.3 (12.9)	0.34	−5.3 (17.3)	12.4 (15.4)	0.01*
Isokinetic knee torque flexion (Nm)	3.7 (8.6)	7.4 (11.4)	0.34	−1.1 (7.8)	5 (7.3)	0.07
Maximal Voluntary Contraction (isometric) (Nm)	6.6 (11.0)	8.7 (14.7)	0.67	4 (16.9)	16.6 (19.7)	0.12
Endurance test at 80% MVC (sec)	−7.4 (12.0)	5.7 (17.0)	0.09	1.5 (11.5)	1.8 (17.4)	0.96
Descending stairs (sec)	0.5 (3.6)	2.5 (7.2)	0.43	−0.09 (1.3)	0.7 (1.7)	0.20
Climbing stairs (sec)	0.3 (1.8)	1.1 (5.8)	0.66	−0.01 (1.2)	0.7 (1.4)	0.18
Standing up from a chair (sec)	0.2 (0.8)	1.2 (4.0)	0.40	0.05 (0.3)	0.2 (0.5)	0.32
Standing up from lying supine (sec)	0.5 (2.2)	−0.4 (1.4)	0.11	0.1 (0.5)	0.3 (0.6)	0.44
Walking 6m (comfortably) (sec)	0.5 (0.8)	0.3 (0.8)	0.52	0.3 (0.7)	1.0 (0.5)	0.01*
Walking 50m (fast) (sec)	3.5 (5.8)	2.7 (6.3)	0.75	0.3 (2.9)	2.2 (2.8)	0.10

NOTE. Positive values indicate improvement.
* $p < 0.05$.

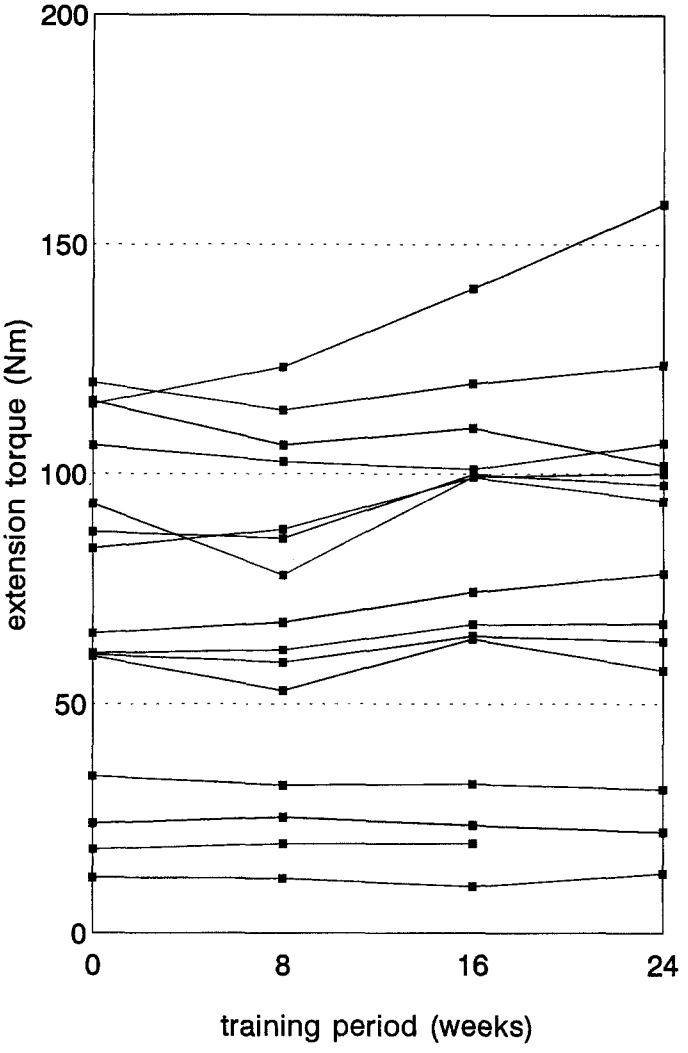

Fig 1—MyD, training group. Mean knee peak extension torques for each subject at the four test sessions.

concerned activities that the participants believed to be related to leg function (table 4). Categories mentioned by fewer than 25% of the participants in one of the two diagnostic groups are not reported. None of the items showed a statistically significant change, even if only the most important leg-related activity was used for each participant (data not shown).

In the training groups, 4 out of 14 MyD subjects (28%) and 7 out of 15 HMSN subjects (46%) reported that they were able to perform an increased number of activities, whereas only 1 MyD and 2 HMSN subjects in these groups reported a decreased number of activities. 4 out of 18 MyD (22%) and 2 out of 13 HMSN (15%) subjects from a control group reported a decrease, whereas only 1 MyD and no HMSN subjects in a control group observed an increased number of activities. 22 MyD patients and 17 HMSN patients did not notice any change over the 24 weeks.

The global assessment did not show a significant change, except for 2 questions in MyD patients: "How were your complaints last week" and "I am less hindered in daily activities because of my strength reduction" (table 5).

Both training groups were positive about the training: 9 (64%) MyD and 13 (93%) HMSN patients believed that they had derived benefit from the exercises; 11 MyD and 12 HMSN patients intended to continue exercising in some way.

Muscle Fibre Membrane Permeability

Initial mean Mb was significantly higher in the MyD group than in the HMSN group (table 6). The difference in Mb levels before and after the measurement session was also higher in the MyD group. At t24 these differences showed no significant change (table 6).

DISCUSSION

This study is the first clinical trial to evaluate systematically the effects of strength training in the most common slowly progressive hereditary neuromuscular disorders: myotonic dystrophy and HMSN.

Remarks on the Conditions of the Trial

Drop out. Drop out during the trial was very low. This may be partly because patient selection and motivation; the qualification period appears to have been very useful for this purpose.

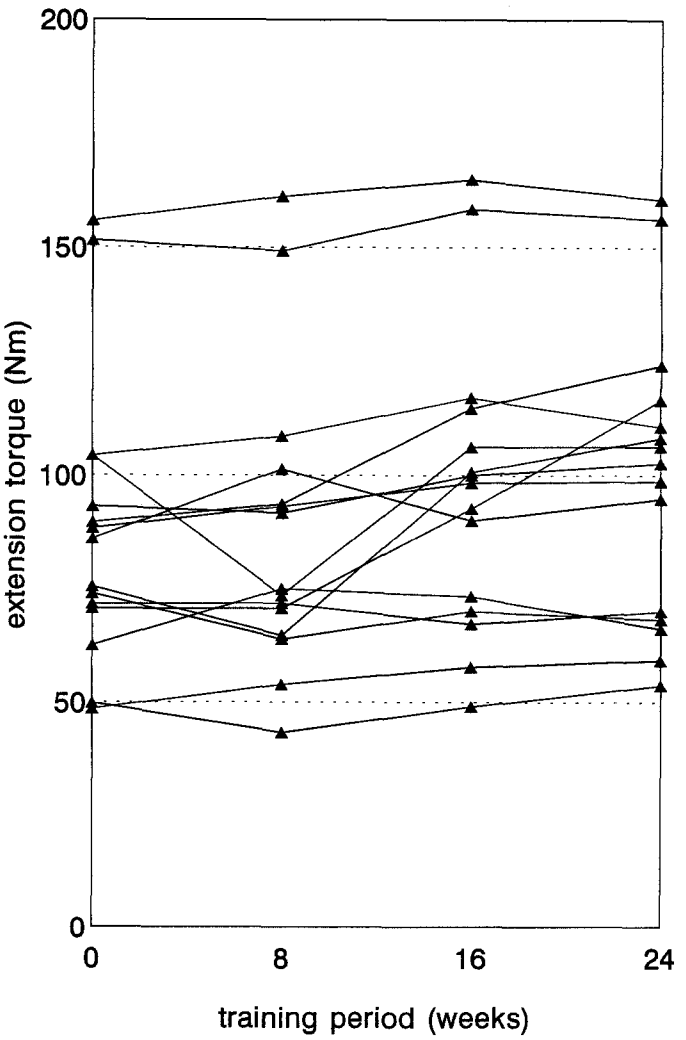

Fig 2—HMSN, training group. Mean knee peak extension torques for each subject at the four test sessions.

Table 4: Problem Elicitation Technique. Numbers of Times That Problems in the Various Categories Were Mentioned at t0

	MyD (n = 33)	Leg Related	HMSN (n = 29)	Leg Related
Walking outside	19	19	16	15
Sports	17	7	14	13
Work outside	14	5	15	9
Stair-climbing	13	13		
Housekeeping	11	3	9	3
Housecleaning	9	3	8	6
Acceptance	8		9	
Need to sleep	14			
Ortheses/shoes			10	10
Leisure activities	9	2		
Anger	8			
Mobility			7	4

NOTE. Subjects were asked whether they believed that the problem was to be caused by impairments of the leg or of other body parts.

Group composition. Comparability of training and control groups was very good in the HMSN group. The comparability in the MyD group was suboptimal because the training group (1) contained more women, (2) was somewhat older, (3) had longer time scores for stair climbing, and (4) had higher knee torques. This may have biased the results: The first three items could have resulted in an underestimation, whereas the high knee torques could have resulted in an overestimation of the training effects. Overall differences in group composition do not seem to explain the absence of changes in the MyD group.

The SIP of the MyD patients showed the same profile as in a recent Dutch national survey.[40,41] Therefore, it appears logical to generalize these findings to the entire population of MyD patients.

Compliance. Training loads could be increased in both patient groups.[44] This is in agreement with other studies.[4,7-13] It can be concluded from this increase that training compliance was good. In view of the performance in the exercises and the training diaries, the therapists also had the impression that motivation was good in most participants. It is not completely certain that the controls refrained from training. However, the authors gave strict instruction during the qualification period. In combination with the information from the interview with each individual participant after finishing the trial, the authors arrived at the conclusion that training did not significantly influence performance of patients in the control groups.

Blinding. Blinding of the patients was impossible. This may have influenced some results; in particular it could explain the diminished endurance time in the MyD control group and the shorter time scores for walking 6m in the HMSN training group. In addition, the answers to the questionnaires may have been influenced. However, because most changes are reported on items known to be mainly related to leg function, the authors believe that the questionnaire answers reflect a real change, at least in the HMSN patients.

Blinding of the observers was assessed after the last measurement session. In 20% of the cases, the observer was sure about the treatment allocation because the patient accidentally gave away this information. For the other subjects kappa was low, which shows a rather good blinding.

Table 5: Items From Global Assessment Questionnaires

	MyD	HMSN
Complaints last week	0.05*	1
Well-being	0.07	0.83
Overall functioning	0.09	0.77
Feeling strong	0.11	0.68
Hindered by strength reduction in daily activities	0.02*	0.85

NOTE. Changes in scores between t0 and t24 expressed as p values (paired t test).
* $p \leq 0.05$.

Table 6: Serum Myoglobin (ng/L). Differences Between MyD and HMSN and Between Control and Training Groups

Differences between MyD and HMSN (t test)

	Initial Value at t0	Increase Due to Test Session at t0
MyD (n = 31)	235 (125)	31 (39)
HMSN (n = 28)	96 (62)	10 (27)
p =	0.000	0.02

Differences between control and training groups*

	Group	Initial Value at t0	Increase Due to Test Session at t0	Initial Value at t24	Increase Due to Test Session at t24
MyD	control	263 (149)	41 (42)	248 (120)	28 (28)
	training	203 (84)	20 (34)	175 (74)	26 (35)
HMSN	control	99 (75)	7 (16)	94 (54)	25 (70)
	training	93 (51)	12 (35)	113 (70)	15 (96)

* All changes between t0 and t24 were nonsignificant.

Interpretation of Outcome Measurements

In both patient groups baseline data on knee torques and timed motor performance differ significantly from those for healthy subjects.[36]

Strength. The MyD group showed no relevant change in knee torques as a result of the training. In contrast to reports of other authors[45,46] no signs of overuse were found. The small nonsignificant training effect in the stronger patients is in agreement with the suggested relation between initial strength and trainability in a mix of neuromuscular patients.[8]

Knee torques in the HMSN group showed a significant increase. The percentage of improvement was moderate compared with strength increases found in healthy persons after comparable training.[27,47] Initial strength is known to be reduced in HMSN.[36] This strength reduction may result from the disease itself or from disuse, eg, because of foot complaints. Subjects with disuse atrophy are known to show a much stronger increase in strength after training than was found in these patients.[48] It is therefore believed that if only disuse had a major impact on performance in these patients, training would have resulted in a higher increase of torques.

Fatiguability. Fatiguability is high in many neuromuscular disorders.[49-51] The torque at which the endurance test had

to be performed at all measurement sessions was based on the MVC of that individual at t0. Therefore, an increase in endurance time could be expected with increasing strength. However, this was not found. The reliability of the endurance measurement may have been poor because the time depends strongly on motivation.

In the MyD group, endurance time showed a decrease mainly in the control group. Whether this decrease resulted from progression of the disease or from lack of motivation is unclear. In the training group mean endurance time did increase, although the increase was statistically nonsignificant. In the HMSN group, endurance time did not change, although torques increased. The poor reliability of endurance measurement might explain the absence of changes in time.

Functional ability. Functional abilities as measured by time scored activities showed no change in either of the patient groups. For the MyD patients this can be explained by the lack of change in torque. Only the speed of *natural* walking showed a significant increase in the HMSN training group. It is assumed that this test was influenced most by motivation. Hence, only tests that have to be performed at maximal speed appear appropriate for evaluation if the subjects cannot be blinded for treatment allocation. The change in the other time scores in HMSN patients was not statistically significant. This may be caused by (1) the weak relation between time scores and knee torques in this group,[36] (2) other impairments (like contractures and sensory disturbances) influencing functionality,[52] and (3) specificity of training, which precludes a generalization of training effects to other tasks.

Questionnaires. Questionnaires about leg function showed a change for a few items in the MyD group. This is in agreement with the minimal torque changes. The HMSN group showed an improvement on items that are strongly related to upper leg strength (eg, ascending stairs and getting into and out of a car). Patients stated that they experienced less difficulty in performing such tasks.

Because all changes in time scores were in favor of the training groups, and because of the subjective increase in performance in HMSN, a clinically relevant effect is suggested, although the findings were not statistically significant. Changes in torques and VAS scores were not correlated. This may be because of (1) variability in the translation of subjective feelings into VAS scores or (2) psychological phenomena that might influence the VAS scores more than real changes in motor performance. However, because significant changes were only reported on items that are known to be related to lower limb function and because the patient group with the greatest changes in torques reported the greatest subjective improvement, it is believed that the subjective improvement is real. Moreover, improvement of functionality does not always result in lower time scores.

Activities that patients considered to be most important in their daily life (as measured by the PET) were more often related to leg function than to arm or back function. No changes were observed in the answers to the questions about these activities, neither in the MyD nor in the HMSN group. On the global assessment questionnaires, MyD patients in the training group stated that they felt better and were less hindered by their strength reduction. One can only guess what the explanation for this subjective improvement might be. Perhaps these patients were more able to deal with their strength reduction because participating in the exercises had made them more aware of it. Another explanation could be that other trained but unevaluated muscles increased in strength and that these muscles were the relevant ones for the improvement. The HMSN training group did not report any subjective improvement. It is interesting that the MyD subjects, who showed less objective change in strength, showed much more significant improvement in the global self-assessment items, whereas the HMSN subjects, who showed greater objective improvement in strength, did not show any significant change or improvement on the global assessment items.

Membrane permeability. Muscle fiber membrane permeability was assessed by measuring serum Mb. Mb was measured before and at 1 hour after the measurement sessions because Mb rises within 1 hour after exercise.[42,53] Changes in serum enzyme activity after a standardized test reflect changes in muscle fiber membrane permeability.[54]

Creatine kinase (CK) is the muscle enzyme usually studied, but in MyD, Mb concentrations appear to be a more sensitive parameter than CK activity for evaluating muscle fiber membrane permeability.[53] The authors, as well as others,[55-57] found elevated mean initial values of Mb in MyD. In addition, a large Mb increase over the measurement session was observed in the MyD group. CK does not increase in MyD after ischemic exercise tests.[58] This may be explained by the lower molecular weight of Mb. Fiber membrane permeability appears to be elevated especially for smaller molecules in MyD; this permeability did not change as a result of the training.

Initial Mb levels were normal in the HMSN group. The increase because of the standardized test protocol did not show any changes in muscle fiber membrane permeability as a result of the training. Muscle damage leads to an increase in muscle fiber membrane permeability. Pain, especially if related to weakness, is also considered to be a sign of muscle damage. In healthy subjects, such complaints, considered to be a sign of muscle damage, often precede an increase in strength; the muscle damage is a temporary phenomenon. Some patients had complaints suggesting overuse at the start of a new 8-week training period. After the first training period a few subjects complained of muscle soreness and a transient strength reduction at t8. However, no signs of muscle damage were found over the entire period of 24 weeks.

Considerations for Patient Care

Changes on all measurement tools were in favour of the training groups, suggesting clinically relevant effects, although they were often statistically nonsignificant. Most participants of both training groups stated that they had enjoyed the training and intended to continue exercising in some way. Many MyD patients show a serious loss of strength and functionality. The data suggest that trainability was poor in the more seriously impaired patients. This is in agreement with the findings of other authors.[59] Because of the lack of negative training effects so far and because of the relation between trainability and initial strength, the authors argue

that it is worthwhile to try and optimize muscle function at an early stage. Strict evaluation is needed.

Although clinical examination of proximal muscle groups showed no substantial weakness, HMSN patients were found to have decreased knee torques and also increased timed motor performance.[36] These patients gained strength by training, but the gain in functional performance was marginal. Because functional improvement is the ultimate goal of interventions, the authors advise combining strength training with functional training. This training has to be tuned to the functional status of each individual and the demands of that individual in daily life.

Considerations for Future Research

The usefulness of strength training will differ for many neuromuscular diseases (as was also found in this study), because of differences in pathophysiology. Therefore, research on groups with a variety of neuromuscular disorders is not a sensible approach.

Because of the suggested relation between trainability and initial strength in MyD, it appears worthwhile to start strength training and/or functional training as soon as the diagnosis has become clear. Research into the long-term effect of such an early stage intervention is needed.

This trial was confined to 6 months of training, three times a week, at 60% to 80% of RM. Because no signs of overwork weakness were observed, future research with more intense and longer training programs appears to be indicated.

What is needed is not only strict evaluation at the level of the intervention, but also evaluation of its consequences for functionality. Adequate measurement tools can only be chosen after further research giving insight into the factors determining functionality.

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