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Review Article

Effects of Conventional Therapy on Quality Of Life in CMT Disease Review and Meta-Analysis

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Abstract

Objectives: Up to now, only symptoms of Charcot-Marie-Tooth disease can be treated. This work investigates which therapy is the most effective in Quality of Life in Charcot-Marie-Tooth.
Methods: A literature research was conducted (search terms “Whole Body Vibration” or “WBV” or “Exercise” or “Rehabilitation” and “Charcot Marie Tooth” or “CMT” or “Hereditary Neuropathy” or “HMSN”) in five online databases. Inclusion: Publications from January 1990 to April 2022. Exclusion: No conventional treatment or Charcot-Marie-Tooth. Methodological quality: assessed by PEDro score. Effect sizes: calculated by Standardized Mean Differences and 95 % Confidence Intervals.
Results: Of the 5,941 publications found, 17 focused conventional treatment for Charcot-Marie-Tooth disease of whom four had a good quality and investigated Quality of Life. No study investigates Whole Body Vibration. There is no effect (SMD = .29) in health related Quality of Life, a low effect (SMD = -.42) in Activities of Daily Living favoring experimental groups and no effect (SMD = .13) in Disability favoring control groups.
Conclusions: These interventions cannot improve Quality of Life in Charcot-Marie-Tooth. Since no studies investigated "Whole Body Vibration" in Charcot-Marie-Tooth, this should be done as well as a motor ability training program. Such studies are in planning.

Keywords: Charcot-Marie-Tooth; Hereditary Motor and Sensory Neuropathy; Rehabilitation; Exercise therapy

Introduction:

Charcot-Marie-Tooth disease (CMT) is the most common neurogenetic disease. Between 20 and 30 persons per 100,000 of population are affected. It is mostly an autosomal-dominant hereditary condition. Therefore, there are clusters in individual families. In most cases, the cause is a mutation on chromosome 17. CMT is a hereditary disease of peripheral nerves. The nerve cell axon, the insulating myelin layer is damaged by a gene mutation. The myelin acts like plastic insulation around an electrical cable. In the disease, saltatory conduction of excitation, i.e., the transmission of nerve impulses in peripheral nerves, is impeded. As a result, commands from the brain do not reach the muscles or do not reach them properly. Denervation results in weakness and degradation of the affected muscles. Typical early symptoms include weakness or paralysis of the foot and lower leg muscles, which can lead to difficulty lifting the foot and a high-heeled gait with frequent stumbles or falls. Affected individuals also have balance problems. Foot deformities are also common in CMT. As the disease progresses, weakness and atrophy in the hands can cause difficulty with fine motor skills. Degeneration of sensory nerve axes can lead to a decreased ability to feel heat, cold and tactile sensations. Proprioception is often diminished in people with CMT. The condition can also cause curvature of the spine (scoliosis) and hip displacement. Many people with CMT develop contractures, which prevents joints from moving freely. Muscle spasms are common. Nerve pain can range from mild to severe. Some people rely on foot or leg braces or other orthopedic devices to maintain mobility. Progression of symptoms is gradual. The gene mutations in CMT are inherited in three different patterns: autosomal dominant, autosomal recessive and X-linked, all of which are linked to a person's chromosomes (1;2).

There is currently no cure for CMT, but physical and occupational therapies, orthopedic devices, and orthopedic surgery can help sufferers manage the disabling symptoms of the disease. In addition, people with severe nerve pain may be prescribed pain-relieving medications. It is important to maintain mobility, flexibility and muscle strength. Starting a treatment program early can delay or reduce nerve degeneration and muscle weakness before disability occurs. Physical therapy includes strength training, stretching, and moderate aerobic exercise. A specific exercise program prescribed by a doctor can help improve endurance and maintain overall health. Many people with CMT need orthotics and other orthopedic devices to help maintain daily mobility and prevent injury. Bandages can help prevent ankle sprains by providing support and stability during activities such as walking or climbing stairs. Thumb splints can help with hand weakness and loss of fine motor skills. Such aids should be used before disability "occurs" because they can prevent muscle strain and reduce muscle weakness. Some people with CMT opt for orthopedic surgery to treat severe foot and joint deformities, improve walking ability, and relieve pain. Occupational therapy involves learning new ways to manage activities of daily living (2). A special form of exercise therapy is "Whole Body Vibration" (WBV) training. Many positive effects on various parameters have been reported for WBV, such as increased muscle activity, improved posture, and improved blood circulation in the legs (3;4;5;6;7). WBV is used since a few years in the exercise therapy for neurological diseases, such as stroke, Parkinson's disease or in diabetic neuropathy, as a few review can show (8;9;10). There are few side effects and contraindications known (11;12). Since WBV is such a smooth form of therapy, it could also be used for CMT.

Many studies have already been conducted to understand the positive effects of different treatment methods (exercise therapy, orthosis etc.) in CMT patients (13;14;15). Therefore, in this study it is aimed to understand which method is the most effective in the treatment on different aspects of Quality of Life in CMT.

Materials and methods:

This work followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A literature search was performed using PubMed, PEDro, OVID, Cochrane Library and Science Direct databases using the search terms in combinations "Whole Body Vibration" or “WBV” or “Exercise” or “Rehabilitation” and "Charcot-Marie-Tooth” or “CMT” or “Hereditary Neuropathy” or “HMSN”. Only original studies that investigated such conventional treatment for CMT patients were included. All publications from January 1990 up to April 2022 were included. There were no limitations in language, age of participants, or study characteristics (e.g., vibration frequency, single session, or long term). Studies that did not have WBV as a treatment or CMT as the treated disease, or animal participants were excluded. The PEDro score was used to determine methodological quality of the included studies. Selection and data collection were conducted by both authors. The methodological criteria were evaluated among both authors. In the case of disagreement, results were discussed and consent was found.

RevMan 5.4 software was used for the meta-analysis. Funnel plots using the Egger test for publication bias were created (16). Standardized mean differences (SMD) and their 95%-confidence intervals (CI) were calculated, and classified as small (SMD > 0.3), moderate (SMD > 0.5), and large (SMD > 0.8) effects (17). SMD and CI are presented as forest plots. Random-effects model meta-analyses were also used, as the effects varied across studies. I^2 was used to assess heterogeneity between studies because I^2 can be calculated and compared across meta-analyses of different study sizes and types and can included different types of outcome data. The magnitude of heterogeneity was categorized into the following categories: low heterogeneity (I^2 =25%), moderate heterogeneity (I^2 =50%), and high heterogeneity (I^2 =75 %) (18;19).

The following outcomes to assess different aspects of Quality of Life are used for the meta-analysis:

Activities of Daily Living

- *Time scored activities:* good psychometric properties, consisting of the tasks Descending stairs, Climbing stairs, Standing up from chair, Standing up from lying (20)
- *Timed up and Go (mobility):* good psychometric properties, consists of the tasks standing up from a chair, walking 3 m, turn around, walking back and sitting down on the chair. Time is taken for the whole course (21)

Disability

- *CMTES:* Charcot-Marie-Tooth Examination Score, subscale of the CMT Neuropathy Score, has good psychometric properties, consists of the parameters sensory symptoms, motor symptoms legs and arms, pinprick sensibility, vibration, strength legs and arms, ulnar CMAP, and radial SAP amplitude (22)
- *CMTPedS:* Charcot-Marie-Tooth Pediatric Scale, has good psychometric properties, consists of the subscales hand dexterity (Functional Dexterity Test, Nine-hole peg test), Strength (hand grip, foot plantarflexion and dorsiflexion in N), sensation (pinprick and vibration), balance (standing feet apart on a line with eyes open and closed, one leg stance with eyes open and closed, one leg stance on a beam with eyes open and closed, walking forward on a line, walking forward on a line heel to toe, standing heel to toe on a beam) (23)
- *FSS:* Fatigue Severity Scale, questionnaire with good psychometric properties, consists of the items motivation is lower when I am fatigued, exercise brings on my fatigue, I am easily fatigued, fatigue interferes with my physical functioning, fatigue causes frequent problems for me, my fatigue prevents sustained physical functioning, fatigue interferes with carrying out certain duties and responsibilities, fatigue is among my three most disabling symptoms, fatigue interferes with my work, family, or social life (24)
- *VAS:* Visual Analog Scale for pain, good psychometric properties, excepting criterion validity, consisting of a scale from 1 (low pain) to 10 (high pain) points (25)

Health related Quality of life

- *SF-36:* Health Survey Short Form-36, good psychometric properties, consisting of the subscales physical functioning (vigorous and moderate activities, lift or carry groceries, climb one or several flights, bend or kneel, walk mile, walk one or several blocks, bathe or dress), social functioning (social-extent, social-time), role limitation – physical (cut down time, accomplished less, limited in kind, had difficulty), role limitation – emotional (cut down time, accomplished less, not cheerful), mental health (nervous, down in dumps, peaceful, blue/ sad, happy), vitality (Pep/ life, energy, work out, tired), bodily pain (pain-magnitude, pain-interfere), general health (general health rating, sick easier, as healthy, healthy to get worse, health excellent), health changes (26)
- *CHQ:* Child Health Questionnaire for parents, good psychometric properties, consists of the items general health, limitations in energy taking activities due to the health problem, limitations in school works or activities with friends due to emotional or physical problems, bodily pain magnitude and interfere, arguing a lot, concentration difficulties, lieing or stealing, behavior rating, feeling like crying or lonely, nervous, bothered or cheerful, satisfaction about different life aspects, health compared to peers, health compared to one year ago, limitations or interruptions in family activities because of the child’s problem, general family’s ability to get along with one another, emotional worry about child’s problem, limitations in time for own needs because of the child’s problem (27).

Results:

Table 1 provides the results of the searching strategy using the mentioned search terms.

Table 1: Results of the searching strategy using the search terms "Whole Body Vibration" or "WBV" or "Rehabilitation" and 'or "Exercise""Charcot-Marie-Tooth" or "CMT" or "Hereditary Neuropathy" or "HMSN".

Combination of search terms	Number of publications found
Rehabilitation and Charcot Marie Tooth	660
Rehabilitation and CMT	665
Rehabilitation and Hereditary Neuropathy	824
Rehabilitation and HMSN	452
Exercise and Charcot Marie Tooth	521
Exercise and CMT	1,052
Exercise and Hereditary Neuropathy	1,189
Exercise and HMSN	214
Whole Body Vibration and Charcot Marie Tooth	45
Whole Body Vibration and CMT	182
Whole Body Vibration and Hereditary Neuropathy	112
Whole Body Vibration and HMSN	14
WBV and Charcot Marie Tooth	2
WBV and CMT	3
WBV and Hereditary Neuropathy	6
WBV and HMSN	0

The figure 1 presents the PRISMA flow diagram of the study process.

A total of 5,941 publications were identified in the initial literature search. After title screening, 1,989 duplicates and 3,104 publications that did not investigate CMT or conventional therapy for CMT were removed. Following the screening process, 82 publications remained, of which were 17 original studies with human participants.

Table 2 provides an overview of the 17 included publications and their findings.

Table 2: Overview of the study characteristics (1RM = one repetition maximum, CG = control group, CMT = Charcot-Marie-Tooth disease, CMTPedS = Charcot-Marie-Tooth disease Pediatric Scale, CoP = Center of pressure, CT = controlled trial, DT = double task, EG = experimental group, IBM = inclusion body myositis, LGS = limb-girdle syndrome, MMD = myotonic muscular dystrophy, NR = not randomized, PEDro = PEDro total score, PET = Problem Elicitation Technique, RCT = randomized controlled trial, ROM = range of motion, VAS = visual analog scale, WOMAC = Western Ontario and McMaster University Osteoarthritis Index)

Author/s, year	Participants	Design	Intervention	Outcomes	Results	PEDro
Burns et al., 2017, (27)	CMT (n = 60) 6 to 17 years old 30 EG, 30 CG	RCT	3 x 25 min home based training/ week 6 months (total 72 training sessions), including 12 supervised trainings EG: moderate-intensive, progressive resistance training with adjustable exercise cuffs (50 % to 70 % of 1RM) CG: sham treatment (< 10 % of 1RM)	Measurements: baseline, months 6, 12, and 24: Hand-held dynamometry (isometric dorsiflexion strength) MRI (muscle and intramuscular fat volume) CMTPedS (disability, gross and fine motor function, strength, sensation, and balance)	Increased strength in EG, decreased in CG after 24 months, no effect during intervention time No group difference in muscle and intramuscular fat No group difference in disability, gait and ankle stability In Global Impression of Change score more children in EG than in CG are stable or better	9

Cherriere et al., 2020 (28)	CMT (n = 9) 7 to 12 years old 5 EG, 4 CG	CT	2 x 60 min/ week 10 weeks (total 20 training sessions) EG: Adapted dance program (warm-up, various dance forms, stretching) CG: no intervention	Measurements: baseline, week 10 VAS (pain) CMTPedS Dynamometry (muscular force and power) Force platform (muscular force and power, postural control) Mira Stambak 21Rhythmic (rhythm) Score! and Score DT (sustained attention) Digit span (short term and working memory)	Reduction of pain during intervention Significant improvement in CMTPedS, muscle strength and 21Rhythmic in EG	5
Dahl et al., 2004 (13)	47 children, 40 adults Congenital myopathy (n = 3) Duchenne muscle dystrophy (n = 5) Myotonic dystrophy (n = 11) Congenital myotony (n = 4) LGS (n = 9) Muscle dystrophy, not specified (n = 12) CMT (n = 21) Dejerine-Sotta disease (n = 2) Neuropathy, unknown (n = 1) Spinal muscle atrophy (n = 11) Fascioskapulohumeral muscle dystrophy (n = 3) Friedreich-Ataxia (n = 1) MMD (n = 3)	RCT	12 weeks, 2 to 4 sessions of 30 to 45 min/ day, physiotherapy, physical skills, coping strategies, understanding and inspiration further activity in the home environment EG: sessions in Lanzarote CG: sessions in Norway	Measurements: baseline, week 12, follow up weeks 24 and 36 Adults: VAS, 1-6 scale (pain) Beck's Depression Inventory (depression) Quality of life Life Satisfaction Scale Fatigue Severity Scale Ursin Holger Inventarium (symptoms) ADL-Index (activities of daily living) Rivermead Mobility Index (mobility) 20 m walking (walking function) 6 min walking/ wheelchair test (endurance) Timed up and go (mobility) Dynamometer (hand strength) Children: Functional assessments Joint angles (hip/ankle) Ability to move Walking function Pediatric Evaluation of Disability	Significant result for depression in EG	2
Dudziec et al., 2019 (29)	CMT1A (n = 14)	RCT	12 weeks home based training EG: Balance exercises, strength training, falls management session CG: falls management session	Measurements: baseline, week 12 Reported falls and activity over 20 weeks Static and dynamic posturography (CoP), Berg Balance Score, BESTest, Functional Gait Assessment (balance) Lower limb strength test Subjective measures of balance confidence and function	Greater delays with completing the study for EG compared to CG No group difference in reported falls Greater effects for EG in all balance tests than for CG Moderate improvement in COP velocity for EG Small improvement in balance confidence in EG	4

Kilmer et al., 1994 (30)	CMT1A (n = 2) MMD (n = 5) LGS (n = 3) Healthy persons (n = 6)	EG/ CG NR	12 weeks, 3 to 4 x/ week Alternating from 1 to 5 sets with 10 reps Strength training at 12 RM weight with adjustable ankle and wrist cuffs EG: patients CG: healthy persons	Measurements: baseline, weeks 4 and 12 Force transducer (isometric strength of elbow flexion and knee extension) Dynamometer (isokinetic concentric an eccentric elbow flexion and knee extension: peak torque and work per degree)	Significant group differences in knee extension parameters isometric peak torque, isokinetic peak torques and in elbow flexion parameters isometric peak torque, concentric isokinetic peak torque and isokinetic work per degree No comparison between patients reported	3
Lindeman, & Drukker, 1994 (31)	CMT (n = 29, 15 EG, 14 CG) MMD (n = 33, 15 EG, 18 CG) adults	RCT	24 weeks, 3 x/ week EG: Strength training for leg musculature (knee extensors and flexors) with adjustable weights (weeks 1 to 8 at 60 % of 1RM, weeks 9 to 16 at 70 % of 1RM, weeks 17 to 24 at 80 % of 1RM) CG: No intervention	Measurements: baseline, week 12 Dynamometer (isokinetic knee extension and flexion torque, MVC) Endurance time at 80 % MVC (fatigue) Functional abilities (time-scored activities, questionnaires WOMAC, PET, VAS)	Only in CMT patients significant improvements in isokinetic knee extension and flexion torque and MVC, as well as in questionnaires (descending and ascending stairs, rising from sitting, picking up something, from the floor getting in/ out car), no significant changes in time-scored activities	3
Lindeman et al., 1995 (32)	CMT (n = 28, 14 EG, 14 CG) MMD (n = 30, 15 EG, 15 CG) 16 to 60 years old	RCT	24 weeks, 3 x/ week home based training EG: Strength training with 60 % of 1RM 3 sets with 25 reps, 1 min rest between sets (weeks 1 to 8), 70 % 3 sets with 15 reps, 1 min rest between sets (weeks 9 to 16), 80 % 3 sets with 10 reps, 1 min rest between sets (weeks 17 to 24) CG: No intervention	Measurements: baseline, weeks 8, 16 and 24 Dynamometer (strength: maximum isokinetic concentric knee torques and isometric maximum voluntary contraction MVC, endurance: maximum duration of contraction at 80 % of MVC) Functional abilities (time scored activities, modified WOMAC and PET questionnaires	Significant improvement in CMT EG in isokinetic knee torque extension and 6 m comfortably walking	6
Matjacić, & Zupan, 2006 (33)	CMT1 (n = 16) 14 to 60 years old	RCT	12 sessions (6 consecutive days, 1 day rest, 6 consecutive days) Per session 10 min stretching, 10 min strengthening exercises, 20 min balance exercises EG: performed balance exercises standing on a mechanic apparatus (Balance Trainer) CG: performed balance exercises standing on the bottom	Measurements: baseline, day 13 Berg Balance Scale (balance) Up&Go (mobility) 10 m walk (gait)	Significant improvement in both groups in Berg Balance Scale Significant improvement for EG in Up&Go and 10 m walk	6

Mori et al., 2017 (14)	CMT1A (n = 53)	RCT	12 weeks Respiratory, proprioceptive and stretching exercises EG: additional treadmill training CG: no additional training	Measurements: baseline, week 12 and 12-week follow-up 6 min walking test (endurance) 10 m walking test and Walk-12 (gait) Short physical performance battery SPPB Dynamometer (lower limbs strength) Berg Balance Scale (balance) CMT neuropathy score and Medical Outcomes Study Short Form SF-36 (disability)	Week 12: significant improvement in both groups in 6 min walking, 10 m walking, Berg Balance Scale and SPPB Follow-up: still significant improvement in CG in 6 min walking	4
Mori et al., 2016 (34)	CMT1A (n = 53)	RCT	12 weeks Respiratory, proprioceptive and stretching exercises EG: additional treadmill training CG: no additional training	Measurements: baseline, week 12 and 12-week follow-up 6 min walking test (endurance) 10 m walking test and Walk-12 (gait) Short physical performance battery SPPB Dynamometer (lower limbs strength) Berg Balance Scale (balance) CMT neuropathy score and Medical Outcomes Study Short Form SF-36 (disability)	Week 12: significant improvement in both groups in 6 min walking, 10 m walking, Berg Balance Scale and SPPB Follow-up: still significant improvement in CG in 6 min walking	4
Phillips et al., 2021 (15)	CMT1, CMT2 (n = 11) 38 to 74 years old	RCT Cross over	18 weeks (each orthoses 3 weeks plus 1 week wash-out, plus 12 weeks preferred orthoses) EG1: Polypropylene ankle-foot orthoses (PPAFO) EG2: Silicone ankle-foot-orthoses (SAFO) EG3: Ligaflex orthoses	Measurements: baseline, weeks 15 and 28 Goal Attainment Scale (goal achievement) Likert scaled every day use of orthoses (ease of donning and doffing, overall satisfaction) Likert scaled impairment and Borg Scale of Perceived Exertion while walking (pain, comfort) Nottingham Extended Activities of Daily Living questionnaire, Berg Balance Scale, gait analysis (activity and participation)	Significant difference (advantage for PPAFO) in gait parameters stance time (% stride), swing time (% stride), stride length, proportion of expected stride length, velocity, proportion of expected velocity, swing velocity Significant difference in every day use (advantage for PPAFO) in comfort and overall satisfaction	5
Ramdharry et al., 2018 (35)	CMT1A (n = 14, 7 EG, 7 CG)	RCT	12 weeks home based training EG: proximal strengthening and multi-sensory balance exercises CG: no intervention	Measurements: baseline, week 12 Berg Balance Scale and BESTest (balance) 10 m walking, Functional Gait Assessment (gait) Bruininks Oseretsky Test (motor skills)	Strong effects (advantage for EG) in Berg Balance Scale, BESTest, 10 m walk and Functional Gait Assessment Moderate effect (advantage for EG) in Bruininks Oseretsky Test	4

Ramdharry et al., 2014 (36)	CMT (n = 32, 18 EG1, 14 EG2)	RCT Cross over	40 weeks: 16 weeks training/ control condition, 8 weeks wash out, 16 weeks control/ training condition EG: 2 consecutive sets of 8 to 12 reps, 4 x/ week, 40 % to 60 % of MVC CG: no intervention	Measurements: baseline, weeks 16, and 40 MVC hip flexor (peak muscle strength) 6 min walking test (endurance) Modified Physiological Cost test Borg Scale during walking 10 m walking (gait speed) Walk-12 (perception of walking ability) Fatigue Severity Scale (fatigue) Overall Neuropathy Limitations Scale (disability) Phone-FITT Scale (physical activity level)	Significant interaction effect in hip flexor MVC (left side) for training condition	4
Refshauge et al., 2006 (37)	CMT1A (n = 14) < 30 years old	RCT Cross over	12 weeks: 6 weeks per leg Splints adjusted into dorsiflexion (calf stretching)	Measurements: baseline, weeks 6, 12, follow-up week 26 Lidcombe Template (dorsiflexion ROM) Goniometer (eversion ROM)	No significant effect	6
Videler et al., 2011 (38)	CMT (n = 15)	Single group	Neoprene opposition splint for dominant hand	Measurements: baseline, after treatment Sollerman hand function test, Functional Dexterity Test (manual dexterity) Michigan Hand Outcomes Questionnaire, Canadian Occupational Performance Measure (perceived limitations in upper limb function)	Significant improvements in Michigan Hand Outcomes Questionnaire and Canadian Occupational Performance Measure	2

Wallace et al., 2019 (39)	CMT1A (n = 28, 14 EG1, 14 EG2) IBM (n = 17, 9 EG1, 8 EG2) 18 to 80 years old	RCT Cross over	12 weeks training/ control condition, 8 weeks wash out, 12 weeks control/ training condition EG: 3 x 30 min/ week (total 36 sessions) on bicycle ergometer at 60 % of VO_2 peak (weeks 1 to 4), 70 % (weeks 5 to 8), 80 % (weeks 9 to 12) CG: no intervention	Measurements: baseline, weeks 12, 20 and 32 Indirect calorimetry (VO_2 peak) BMI, percentage body fat, blood pressure, lung function Fatigue Severity Scale (fatigue) VAS (pain) Dynamometer (isometric and isokinetic lower limb muscle function) 10 m walking test (gait) 6 min walking test (endurance) Walk-12 Scale Sensewear activity monitor (physical activity) CMT Examination Score (disease specific measures for impairment and disability) Self-efficacy, barriers to activity Short Form 36 Pittsburg Sleep Quality Scale Epworth Sleepiness Scale International Physical Activity Questionnaire	Moderate effect in VO_2 peak for CMT, strong effect for IBM	7
Wright et al., 1996 (40)	CMT (n = 2) MMD (n = 5) LGS (n = 1) 28 to 55 years old	Single group	12 weeks home walking program 3 x/ week, 15 min per session (weeks 1 and 2), 20 to 30 min (week 3), 4 x/ week (weeks 5 and 9) 50 % to 60 % of Reserve Heart rate + Resting Heart rate	Measurements: baseline, week 12, 12 months Graded exercise test (respiratory metabolic pulmonary work capacity) Dynamometer (peak isokinetic torque of knee extensors and flexors) Respirometer (vital capacity, forced expiratory volume in 1 sec, maximum voluntary ventilation) Skinfold caliper (body fat)	Significant decreases in Heart rate and systolic blood pressure	2

In total, four studies investigate the effects of strength training (27;30;31;32), three of strength and balance training (29; 33;35), three of orthosis/ splint wearing (15;37;38), two of stretching exercises (14;34), two of endurance training (39;40), one of physiotherapy (13) and one of dancing program (28). The person samples range from "s" for "ranges" = 8 (40) to n = 60 (27). Intervention duration range from single session (28) to 40 weeks (36). Most of the studies have a duration of 12 weeks (13;14;29;30;34;35;37;39;40). Methodological quality: Five studies are described as “good” (27;32;33;37;39) and can be considered to be included into a meta-analysis. Four of them investigate the effects of conventional therapy methods on different aspects of Quality of Life (27;32;33;39) and are included into meta-analysis. The complete overview of the methodological quality of the included studies, using the PEDro score, can be found in the following table 3.

Table 3: PEDro scores for the studies found

Author/s, year	1	2	3	4	5	6	7	8	9	10	11	Total PEDro score
Burns et al., 2017 (27)	1	1	1	1	1	0	1	1	1	1	1	9
Cherriere et al., 2020 (28)	1	0	0	1	0	0	1	1	0	1	1	5
Dahl et al., 2004 (13)	1	1	0	0	0	0	0	0	0	1	0	2
Dudziec et al., 2019 (29)	0	1	0	1	0	0	0	0	0	1	1	4
Kilmer et al., 1994 (30)	0	0	0	0	0	0	0	1	0	1	1	3
Lindeman, & Drukker, 1994 (31)	0	1	0	1	0	0	0	1	0	0	0	3
Lindeman et al., 1995 (32)	1	1	0	1	0	0	1	1	0	1	1	6
Matjacić, & Zupan, 2006 (33)	1	1	0	1	1	0	0	1	0	1	1	6
Mori et al., 2017 (14)	0	1	0	0	1	0	0	1	0	1	0	4
Mori et al., 2016 (34)	0	1	0	0	1	0	0	1	0	1	0	4
Phillips et al., 2021 (15)	1	1	1	0	1	0	0	0	0	1	1	5
Ramdharry et al., 2018 (35)	0	1	0	1	0	0	0	0	0	1	1	4
Ramdharry et al., 2014 (36)	0	1	0	1	0	0	1	0	0	0	1	4
Refshauge et al., 2006 (37)	1	1	0	1	0	0	1	1	0	1	1	6
Videler et al., 2011 (38)	0	0	0	0	0	0	0	1	0	0	1	2
Wallace et al., 2019 (39)	0	1	1	1	0	0	1	1	0	1	1	7
Wright et al. 1996 (40)	1	0	0	0	0	0	0	1	0	0	1	2

*0: criterion not fulfilled; 1: criterion fulfilled. The items are listed as follows: 1: eligibility criteria were specified; 2: subjects were randomly allocated to groups or to a treatment order; 3: allocation was concealed; 4: the groups were similar at baseline; 5: there was blinding of all subjects; 6: there was blinding of all therapists; 7: there was blinding of all assessors; 8: measures of at least one key outcome were obtained from more than 85% of the subjects who were initially allocated to groups; 9: intention-to- treat analysis was performed on all subjects who received the treatment or control condition as allocated; 10: the results of between-group statistical comparisons are reported for at least one key outcome; 11: the study provides both point measures and measures of variability for at least one key outcome; Total score: each satisfied item (except the first) contributes 1 point to the total score, yielding a PEDro scale score that can range from 0 to 10. Level of evidence: 6 or more of "good" quality, 4–5 of "fair" quality, and below 4 of "poor" quality.

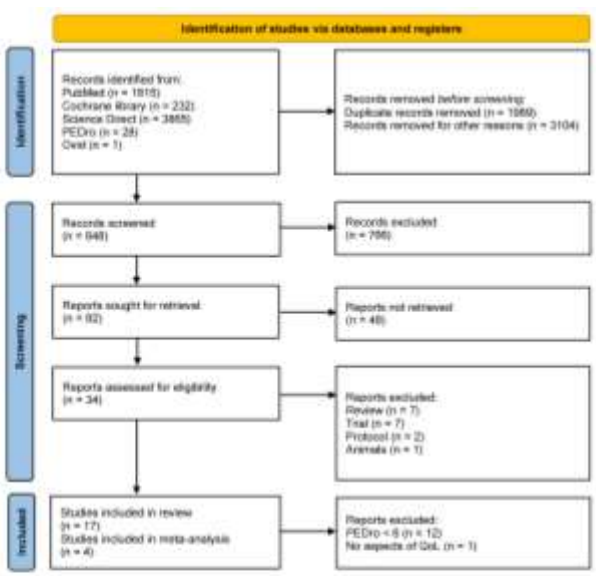

Figure 1: PRISMA flow diagram of the study

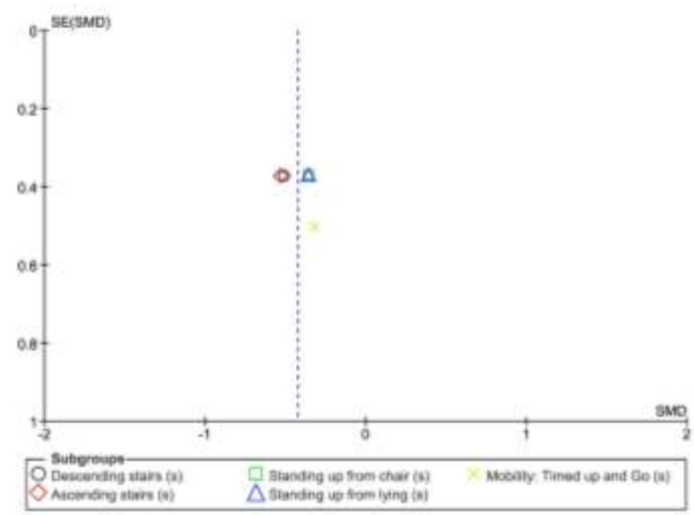

Figure 2: Funnel plot for Activities of Daily Living

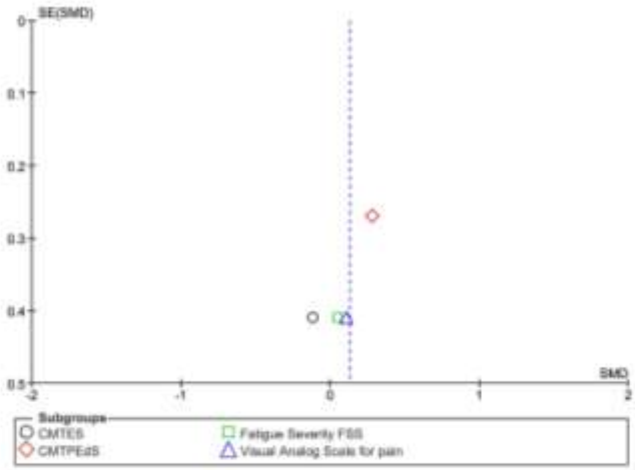

Figure 3: Funnel plot for Disability outcomes

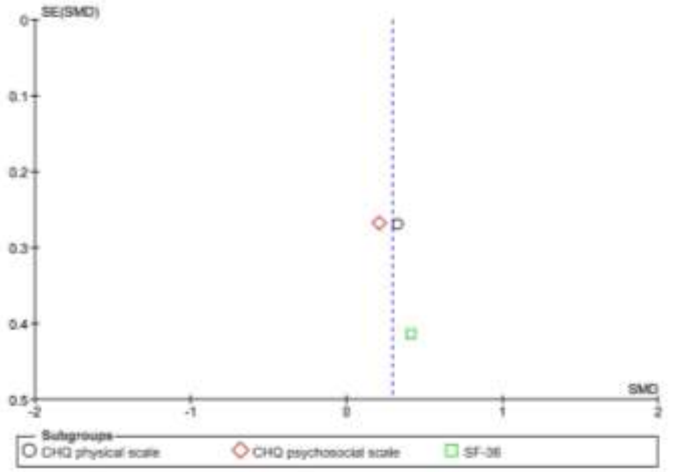

Figure 4: Funnel plot for Health related Quality of Life outcomes

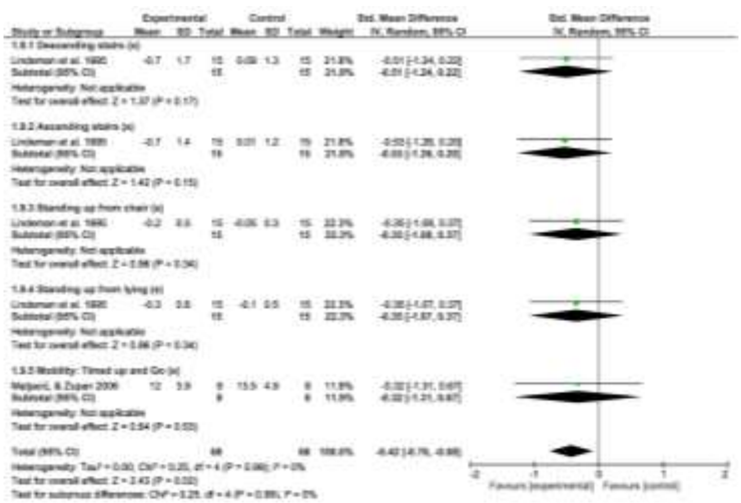

Figure 5: Forest plot for Activities of Daily Living outcomes

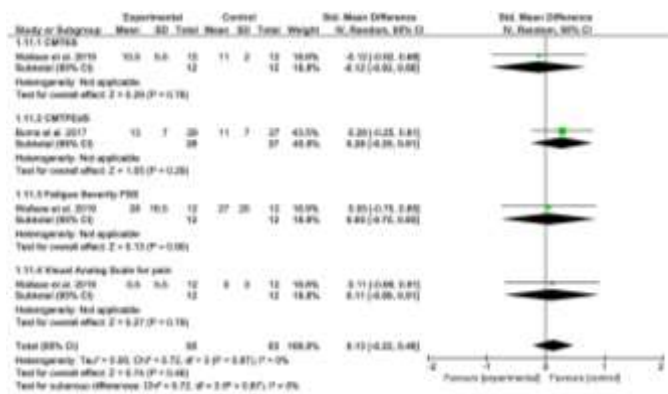

Figure 6: Forest plot for Disability outcomes

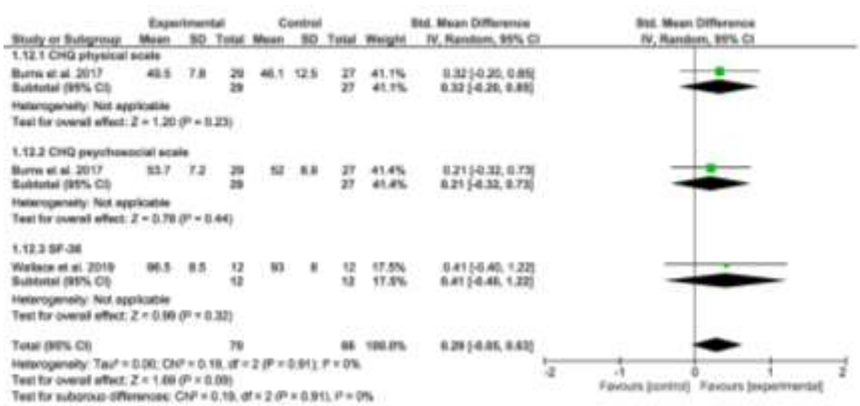

Figure 7: Forest plot for Health related Quality of Life outcomes

Publication bias: Nearly all outcomes are in a homogenous distribution (figures 2 to 4).

"The forest plots (figures 5 to 7) show effect sizes for outcomes of Activities of Daily Living, Disability, and Health related Quality of Life"

Heterogeneity: In all outcomes, an I^2 of 0 % can be found. The Activities of Daily Living outcomes show a non-significant Chi^2 of .25, in Disability outcomes, a non-significant Chi^2 of .72, and in Health related Quality of Life outcomes, a non-significant Chi^2 of .19.

Effect sizes: Effect sizes range from -.53 to -.32 for Activities of Daily Living outcomes (overall effect -.42), from -.12 to .28 for Disability outcomes (overall effect .13) and from .21 to .41 for Health related Quality of Life outcomes (overall effect .29).

Discussion:

Aim of this review and meta-analysis was to investigate which conventional treatments for CMT exist and which of them has the strongest effect on different aspects of Quality of Life. Only five of all studies found had a good methodological quality, of which four investigate the effects of conventional treatments on different aspects of Quality of Life.

Heterogeneity for all outcomes can be considered as low with an I^2 of 0 % and non-significant Chi^2 values.

Overall effects for Activities of Daily Living (SMD=-.42) and Health related Quality of Life (SMD=.29) favor both the experimental groups, in Disability, an overall effect of .13 favors the control group. The overall effects for Disability and Health related Quality of Life are considered as no effects, the overall effect for Activities of Daily Living as small.

In the Activities of Daily Living outcomes, all effects favoring the experimental group can be reasoned by the fact that the study by Lindeman et al. (32) had a “real” control group without any intervention. The other study included here (33) favors experimental group too, but this effect is a bit lower than the others. In addition, this study has the lowest influence on total effect (12 %). Although the Timed up and Go has good psychometric properties, the interpretation of the results is questionable, as shown by a meta-analysis. There are many different cutoff values that are used to decide the risk of falling (41). Furthermore, this test is validated for persons over 60 years of age, the patients of the present study were on average only 38 years old (33), so that the result of this test cannot be correctly classified. Highest effects were found for both stairs tasks in the study by Lindeman et al. (32), lowest effects for the Timed up and Go (33). This could be caused by the difference of intervention durations. The study by Lindeman et al. (32) had a duration of 24 weeks with three sessions per week, the study by Matjacić et al. (33) had a duration of only two weeks with 12 sessions in total. So it can be assumed that this training period was not long enough, even though another study showed that improvements in balance ability and intracortical inhibition were visible after only two weeks of balance training (42).

In the Disability outcomes, the total effect favors control group. This can be reasoned by the fact that there was one study (27) with a sham treatment, favoring control group with an SMD of .28. Because of the number of participants, this study has an influence of about 44 % on the overall effect. The second study (39) included here has nearly no effect, and favors depending from the outcome once experimental and twice in a very low degree control group. In the case of the VAS, it should be noted that criterion validity is questionable (43). Thus, it is not ensured that this scale really captures the severity of pain. Thus, the results of this study should not be taken into account, which would increase the overall effect size in favor of the experimental group. Highest effect favoring experimental group was found for CMTES (39), the highest effect favoring control group for CMTPedS (27). However, the tests that were used here are all questionnaires, so there is a lot of subjective latitude here, since the patients were asked to fill them out and there was no third-person evaluation. However, it can also be assumed that the intervention duration at Burns’ study (27) was too long and thus an opposite effect was produced by fatigue/ overtraining of the patients in the experimental group (44). For the CMTPedS, it should be noted that it has only been validated with a relatively small sample (23). Thus, it is questionable to what extent the results of this validation study can be transferred to the general population.

In Health related Quality of Life, both studies (27;39) favor experimental groups, even if one of them (27) with a placebo condition. Since the CHQ is a questionnaire for parents, but the study does not indicate whether parents knew whether their children were in the experimental or control group, this must be taken into account. For this reason, the sham intervention might not have played a role. The study by Wallace et al. (39) had a stronger effect here than the study by Burns et al. (27). In addition, it could be assumed that endurance training has a more positive effect than strength training, since endorphin response is increased after endurance training, among other things (45) However, it can also be assumed that the intervention duration at Burns' study (27) was too long and thus an opposite effect was produced by fatigue/overtraining of the patients in the experimental group (44).

Conclusions:

It seems that the interventions studied are not successful enough to improve the different aspects of Quality of Life in CMT. This could be due to the type of intervention, but also to the training parameters (e.g. intensity or frequency). It is also possible that the promotion of a single motor ability is not sufficient and that a program needs to be created that promotes all motor abilities (strength, endurance, speed, coordination, flexibility). Another rationale would be that because of the causes of CMT, such treatment does not work

Future directions:

In any case, to improve the different aspects of Quality of Life of CMT patients, further studies must follow. Since no studies on the effectiveness of whole body vibration on the symptoms of CMT are available so far, this gentle method should be investigated as soon as possible, since good results have already been achieved here in other neurological diseases. In addition, the effectiveness of a comprehensive training program that promotes all motor abilities should also be examined. Such studies are in planning.

Supporting information: The PRISMA Checklist.

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Author contributions

Study design, draft, tables and figures: AD; Translation, correction notes on formulations: LMD; Selection and data collection process and evaluation of methodological criteria: AD, LMD; Both authors have made a significant contribution to this study and have approved the final manuscript.

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