

Rehabilitation in Charcot-Marie-Tooth disease type I

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Summary

- Physical therapy and moderate exercise are positively disease-modifying in CMT1A
- Overwork weakness and fatigue need to be considered but should not prevent patients from exercising
- Continuous training at home and repeated rehabilitation measures ensure long-lasting effects
- Biomarkers will facilitate therapeutic trials as well as evidence-based rehabilitation measures

Charcot-Marie-Tooth disease is the most common inherited peripheral neuropathy with a prevalence of approximately 1 in 2,500.¹ The most common subtype is the autosomal dominant type 1A, which is caused by an intrachromosomal duplication on chromosome 17p11.2.^{2,3} A consecutive primary loss of the myelin sheath leads to a secondary axonal degeneration. Characteristic clinical findings include distally pronounced muscle wasting, secondary skeletal deformities, sensory loss and reduced deep tendon reflexes.^{4,5} The individual clinical phenotypes vary, even among monozygotic twins.⁶ They range from sub-clinical manifestations to rare cases of wheelchair-bound patients. Overall, the quality of life is significantly impaired.⁷

Despite ongoing research, no curative treatments are currently available.⁸ A recently published ascorbic acid trial showed no significant effect on the clinical phenotype of CMT1A patients.^{9,32,36} Nevertheless, physical therapy and moderate exercises are proven to be positively disease-modifying. While a cure lies beyond the scope of physical therapy, it may prevent the rapid aggravation of the clinical phenotype.^{10,11,17} Recent studies suggest that CMT patients experience physical as well as mental benefit from rehabilitation programmes, but they also perceive that the performed exercises were not specifically designed to their needs.¹¹ In fact there is little evidenced-based data and no common consensus on rehabilitation in patients suffering from Charcot-Marie-Tooth disease.

Rehabilitation

Overwork weakness and fatigue

The use of physical therapy in CMT used to be a controversial matter in the recent past due to the report of fatigue and overwork weakness.¹² However, a recent study examining the bilateral intrinsic hand and leg muscle strength in 271 CMT1A patients showed no difference between the dominant and the non-dominant side. This

data does not support the hypothesis of overwork weakness in CMT1A and strongly argues for physical activity and rehabilitation.¹³ While fatigue does exist in CMT as in other neuromuscular diseases,¹⁴ it does not necessarily equal to muscle related fatigue, but often as a symptom of energy depletion (Ramdharry et al., 2012). Randomised, controlled studies have previously shown the positive effect of moderate exercise in CMT populations (Chetlin et al., 2004; Lindeman et al., 1995; Carter et al., 2008; El-Abassi et al., 2014). Furthermore, exercising should be encouraged, since a sedentary life-style and secondary weight gain deteriorate symptoms in CMT patients.¹⁹

Bracing

The characteristic pes cavus formation in patients with Charcot-Marie-Tooth disease is due to a plantar flexion deformity of the first metatarsal bone. Initially, an imbalance between the M. tibialis anterior and the peroneus longus was thought to be the cause for foot deformity, but recent findings suggest a selective denervation on the intrinsic foot muscles as the underlying cause.^{20,21} The functional strength can be enhanced by using custom-made ankle-foot orthoses (AFO). They also facilitate stretching and minimise the later development of a neuropathic Charcot joint. Yet, a prospective clinical trial revealed that the range of motion (ROM) and intrinsic strength remain unchanged.^{22,23} When testing the effect of muscle strength in foot dorsal and plantar flexion the use of a dynamometry fixation device is generally recommended.²⁴

Resistance training and creatine supplementation

In an observational clinical trial with 20 CMT patients, the participants received resistance training either with or without additional creatine monohydrate supplementation. After an initial baseline assessment, patients underwent 12 weeks of, mainly home-based, resistance training (3 session/week). The exercises were performed with adjustable wrist and ankle weights, according to the individual baseline strength. Special focus was given to knee extensors / flexors and elbow extensors / flexors exercises. The intensity of training was systematically increased in terms of weight and number of repetitions. Patients tolerated this moderate exercise well and showed high compliance. The training sessions significantly improved the activity of daily life (ADL) and strength. However, no differences in performance were observed when comparing patients with or without creatine monohydrate supplementation.¹⁶ A follow-up study 20-34 months after completion of resistance training showed that patients who

continued as well as patients who discontinued their training, lost strength in comparison to their baseline assessment. The functional abilities on the other hand, were only lost in those who discontinued their training. As a conclusion – despite inevitable loss in strength – functional gains can only be maintained by continuous exercise.²⁵

TreSPE Rehabilitation programme

In a more recent pilot study, patients suffering from several types of CMT underwent a rigorous exercise regimen including treadmill, stretching, respiratory and proprioceptive exercises (TreSPE). The moderate-intensity aerobic exercises were performed twice per week for a duration of two months. After a washout of six months the baseline assessment was repeated. The assessment included a battery of outcome measures, including the MRC scale for lower limb strength, Tinetti Balance scale, Physical Performance Battery, ankle angle, oxygen consumption, complete lung function testing, peak treadmill velocity/slope, time to walk 6m and the Charcot-Marie-Tooth Neuropathy Score. In comparison to a healthy control group, no significant pulmonary differences were observed. Fatigue and overwork-weakness, that would prohibit aerobic exercises in CMT patients, did not occur. Nearly all tested parameters showed improvement after TreSPE, though mainly not statistically significant. The authors partially justify this circumstance with the small number of participants (n=8). Furthermore, they do not recommend usage of the Charcot-Marie-Tooth Neuropathy Score as well as the MRC scale for post-rehabilitation controls, since subtle improvements could not be detected with these measures. However, after 6 months of washout, most clinical measures began to deteriorate again without undercutting the baseline values. Thus, a repetition of TreSPE-training within six months is generally recommended to merely maintain clinical abilities.¹⁰

Quality of Life

Clinical approaches towards the improvement of the conceptual idea of 'quality of life' and mental health in CMT patients are scarce. A recently published meta-analysis of 20 clinical studies on the impairment in 'quality of life', emphasised the need for evidence-based approaches.³¹ Depression, anxiety and sleeping disorders for instance, are significantly more common in CMT patients than in the general population. A holistic approach towards rehabilitation in CMT could therefore include voluntary psychological guidance, coping strategies for sensory loss and neuro-

pathic pain, vocational rehabilitation, as well as genetic counselling.

Outlook: Biomarkers

Despite its monogenetic cause, patients with CMT1A display a marked interindividual variability of disease severity. The underlying reason for this variability is largely unknown and epigenetic factors have been discussed.²⁶ At present, the assessment of the individual disease severity in patients with CMT1A is performed solely by clinical and electrophysiological examinations. The CMT neuropathy score (CMTNS) is a nine item composite scale taking into account sensory and motor symptoms.²⁷ The CMTNS is widely applied as a primary outcome measure in clinical trials.²⁸ The CMTNS ranges from 0 (good clinical performance) to 36 (severely affected) and was reported to increase merely 0.68 points per year in patients suffering from CMT1A.²⁷ An even slower progression was reported within a recent therapy trial with ascorbic acid (0.25 points per year).⁹ In light of the slow disease progression, insensitive outcome measures may increase the risk of false negative results in clinical trials. Recently, we were able to show in a large Europe-wide, clinical prospective study that certain secondary clinical outcome measures, e.g. 10m walking test, nine hole peg test and certain dynamometry measures provide valuable information on the assessment of disease severity in CMT1A-patients and could improve current scoring systems.³⁵ In near future biomarkers will provide powerful tools to monitor therapeutic effects.^{9,29} They could also be used to quantify the effectiveness of applying physical therapy. These Biomarkers may not only serve as sensitive surrogate markers of clinical disease severity, but also identify responders to a putative therapy. CMT rats recapitulate the striking disease variability observed in patients with CMT1A. In a proof of principle study we have demonstrated that the expression levels of selected genes in sciatic nerve and skin tissue can be utilised to measure and predict the disease severity in CMT rats. Importantly, we validated these disease severity markers in skin biopsies of 46 patients with CMT1A.³⁰ At the moment, these markers are examined with regard to disease progression within a large pan-European consortium. In the near future we hope to provide the clinical practice with applicable biomarkers which in turn may accelerate the development of a therapy for CMT1A. Importantly, other sensitive outcome measures including skeletal muscle MRI magnetisation ratios are currently being developed.^{33,34}

Summary

As no curative treatment is yet established for any type of Charcot-Marie-Tooth disease, rehabilitation and physical therapy remain the only positively disease-modifying measures to date. However, much needed evidence-based data on rehabilitation is scarce and former concerns against rehabilitation measures on the grounds of fatigue and overwork weakness can be dismissed in favour of symptom alleviating, moderate aerobic exercises. Even resistance training with light weights on ankles and wrists showed promising results. Due to the slowly progressive nature of the disease, recent studies stress the importance of continuing exercises at home, in order to maintain individual physical abilities. Randomised clinical trials with sensitive outcome measures (e.g. biomarkers) are needed to validate individual rehabilitation programmes for CMT patients. ♦

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Though much needed evidence-based data on rehabilitation is scarce, former concerns against rehabilitation measures on the grounds of fatigue and overwork weakness can be dismissed in favour of symptom alleviating, moderate aerobic exercises

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