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Charcot-Marie-Tooth Disease: Genetic Predisposition and Effect of Resistance Training, Endurance Training, Physical Activity and Orthosis in Attenuating its Severity

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Abstract: Background: Charcot-Marie-Tooth disease (CMT) is the most common neuromuscular disorder presented clinically as peripheral distal sensory and motor neuropathy with longstanding gait difficulty and frequent tripping. Objective: This review assessed a myriad of exercises including resistance training, endurance training, physical activity, and orthosis potentially beneficial for CMT patients. Material & Methods: Literature was searched mainly through electronic journals with the help of search engines (ISI Web of Knowledge, OvidSP and PubMed database). Full text scrutinization of most articles was undertaken while for some articles only necessary abstracts were reviewed. Results: The results showed that all training modalities: resistance training, endurance training, and physical activity in conjunction with orthosis is needed to ameliorate CMT severity and progression. Conclusion: The current literature strengthens the existing paradigm of advantageous effects of exercise in CMT patients with future studies concentrating on microarray gene analysis and fractional protein synthesis are required to further elucidate the pathophysiological and signalling mechanisms of CMT in context of exercise training.

1. INTRODUCTION

CMT is the most common inherited neuromuscular disorder which is presented clinically as chronic indolent peripheral distal sensory and motor neuropathy with longstanding gait difficulty and frequent tripping [1]. It affects approximately 150,000 people in the United States with a prevalence rate of 1 in 3,300 people across the globe [2]. CMT1A is the most widespread demyelinating variant of CMT with an insidious onset in the 1st or 2nd decade of life, most frequently during the 1st 10 years of life [1][2]. CMT1A is associated with PMP22 gene duplication on chromosome 17p11.2 which normally encodes for connexin proteins in humans [1]. Six connexin protein subunits form one connexon unit which combines with other connexons to subsequently form gap junctions. This allows rapid propagation of electrical activity between cells [3]. PMP22 gene also translates for a 22kD protein responsible for synthesizing 2%-5% of myelin by Schwann cells of the peripheral nervous system [4]. The ensuing gene mutation thus impedes the normal physiological nerve conduction resulting in the CMT phenotype i.e. polyneuropathy. Electrophysiological nerve conduction studies are of paramount importance to bolster our understanding about the neuropathic origin of CMT because muscle atrophy changes are a downstream consequence of the disease and therefore cannot be directly assessed using MRI techniques [5]. Clinically, CMT polyneuropathy is categorized into demyelinating and axonal sub-types. A 'demyelination' sub-type is typically ranged at a motor nerve conduction velocity (MNCV) of 15–35 m/s whereas an 'axonal damage' is labelled at MNCV of ≥ 45 m/s [4][6].

2. REVIEW OF STUDIES CITING EFFECT OF DIFFERENT EXERCISE TRAINING MODALITIES ON CMT

Methodology: Literature was searched mainly through electronic journals with the help of search engines (ISI Web of Knowledge, OvidSP and PubMed database). Full text scrutinization of most articles was undertaken while for some articles only necessary abstracts were reviewed.

Introduction: So far, no specific and definitive pharmaceutical treatment is available for CMT, thus a myriad of exercises has been theoretically postulated for CMT patients which includes resistance training (RT), endurance training, physical activity, orthoses, stretching, and postural exercises (e.g. yoga, pilates). Here, we will review the best literary evidence on RT, endurance training, physical activity, and orthosis management of CMT, and analyzing their aftermaths critically.

Effect of RT on CMT: The likelihood of overwork weakness, rapid disease progression and the paucity of methodological techniques make it difficult for researchers to assess the benefits of RT on CMT. For example, to look for safety and efficacy of RT in children (6-17 years) with CMT Burns et al (2017) conducted a randomized control trial (RCT) in Sydney, Australia where pediatric patients performed progressive foot dorsiflexion RT (60%-70% of 1RM; 72 sessions) for six months [7]. He found no evidence of difference for dorsiflexion strength and volume between the patient and sham group at the end of the study [7]. In yet another study, RT performed in conjunction with creatinine supplementation exhibited no additional strength gain [8] and the miniscule muscle hypertrophy and power attained in CMT patients to perform ADL (activities of daily living) typically showed no gender disparity [9]. Moreover, it has been observed that inability to abide to RT consistently ensued a decline in the gained functional strength for CMT patients [9]. These evidences seem true despite a variety of RT regimes used across the globe for both the genders [7][9][10].

Effect of Endurance Training on CMT: The results of most of the studies report an improvement in the balance and postural stability, and diminution in walking disability (better performance and time reduction while covering distance) with endurance training in CMT patients [11][12][13]. For instance, a Danish study (2017) by Knak et al investigated the effect of aerobic training on five adult CMT 1A patients who performed anti-gravity treadmill exercise three times per week for 10 weeks. They found a statistically significant increase in Berg balance; postural stability and six-minute walk test (6MWT) post exercise iterating the urge to replicate and confer these results on a large cohort [11]. Similar beneficial results of anti-gravity training on functional ability have been observed in patients of Becker and limb-girdle muscular dystrophies as well [13]. It's worth noting here that CMT patients respond well to treadmill walking (anti-gravity) if performed in combination with stretching and proprioceptive exercises [13]. The result of these studies showed that both walking on the ground as well as on a normal treadmill was tolerated in CMT patients. However, conflicting results of no improvement in disability profile with aerobic training was seen in one study [6] which urges the need of further studies to evaluate the true magnitude of anti-gravity training on CMT patients.

Effect of physical activity on CMT: The encouraging effects of physical activity behavior on individuals with disability as in CMT is perhaps an uncharted territory for researchers unlike chronic lifestyles ailments such as hypertension and diabetes mellites. For instance, the Kennedy cross sectional case control study (2011) correlated level of physical activity with functional disability and gait-related disability using 6MWT and Walk-12 questionnaire respectively in 50 age and gender matched CMT children in New South Wales, Australia [14]. They found CMT children were significantly less active ($p<0.05$) than their healthy peers and the abovementioned incapacity adversely affected them across their timespan towards adulthood [14]. CMT patients, despite walking lesser number of steps exhibited shorter 'sedentary bouts' and more frequent 'sedentary to active transitions' than their peer matched controls as proposed by the Neurology and Neurosurgery Hospital in London [15]. One possible explanation for this is they move themselves in a variety of other ways than only taking steps e.g. standing. To explicate the perceived potential facilitators and barriers to physical activity, Anens and colleagues [16] correlated CMT with physical activity amongst 44 Swedish males using multiple regression analysis. They found that self-efficacy (facilitator; $\beta = 0.4$) and fatigue (barrier; $\beta = -0.38$) explained 32% variance in physical activity conductance imploring the need to incorporate behavioral interventions such as 'social cognitive therapy' as part of a multidisciplinary management approach for CMT patients [16]. This kind of an insight about physical activity behavior of CMT patients will certainly assist in devising realistic rehabilitation interventions [15].

Effect of Orthosis on CMT: Orthosis is the external application of braces to provide support and align the deformed musculoskeletal system. Despite the paucity of significant scientific evidence several authors consider this rehabilitation modality useful in improving and delaying the clinical severity of CMT. For example, Guillebastre et al (2011) found plastic ankle-foot orthosis (AFO) more relevant for postural stability whereas elastic AFOs appeared more influential for dynamic gait control [17]. A significant 4° increase in range of motion (ROM) was exhibited by Rose et al (2010) in 30 CMT children with serial night casts thus providing ample evidence to augment debate on the use of sophisticated bracing for CMT patients [18]. Also, a conspicuous upsurge in the muscle strength has been reported in the reviewed studies [17][18] despite the fact that different muscle groups were involved in different trials.

Critical appraisal of research elucidating effect of exercise on CMT: It is worth emphasizing here that the existing literature has botched the discussion by not citing the mechanistic basis of benefits of exercise in CMT patients even though the molecular basis of a plethora of anabolic signaling pathways involved in muscle hypertrophy is widely known. Both resistance and endurance training would perhaps upregulate mTOR (mammalian target

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of rapamycin), MAPK (mitogen activated protein kinase), Ca^{2+}-calcineurin, and Phosphatidic Acid pathways thus attenuating clinical symptoms of CMT. By including these findings, researchers could have added weightage to the existing argument [19][20]. Also, the current reviews citing the effect of exercise and CMT is not very strong. This is in part due to the use of subjective methods of assessment (questionnaires, interviews) as well as employing small study samples which diminishes the statistical power of these studies. The use of cross-sectional design by most studies failed to demonstrate a causal relationship between exercise and improvement in CMT symptoms due to lack of temporal sequence. The relatively long latency period of the disease, the vulnerable subject population and the cumbersome ethical considerations remain a challenge for CMT researchers. The transcriptional picture in context of resistance training is relatively less clear as compared to endurance training [20]. Resistance training mainly stimulates transcription of myofibrillar protein synthesis (MyoPS) while maintaining a fine tuning between transcriptome and proteome [20]. This ribosomal translation exhibited a non-specific short-lived increase in 45S pre-rRNA following 3-6 weeks of RT in contrast to more specific and sustainable contractile MPS after 20 weeks of RT [21]. Haun et al challenged this existing paradigm of MyoPS in response to RT and suggested the role of sarcoplasmic proteins upregulation and subsequent hypertrophy, at least during the initial period (~8 days) after high volume RT cessation [21]. With the scarce treatment modalities available, researchers are now looking to treat CMT with gene therapy (inserting functional copy of the faulty gene) and/or stem cell therapy (delivering cells with regenerative potential) [22]. These techniques have not advanced to the clinical trial stage and have been limited to studies in rodents, as stated recently by Kleopa K (Philadelphia, 2019) using a GJB1 gene therapeutic model of CMT1X [23].

3. CONCLUSION AND FUTURE PERSPECTIVE:

To conclude, over the past decade, there are developments in our understanding of CMT in context of both training and rehabilitation still no definitive approach is available for CMT management. The genetic predisposition of CMT makes its management even harder. Existing studies certainly suggest a multi-sectorial approach involving physical activity and exercise in conjunction with orthosis to treat CMT however future studies that elucidate innovative research techniques such as microarray gene analysis and fractional protein synthesis are needed to know more about the potentially relevant pathophysiological and signaling mechanisms of CMT. Also, an elusive understanding of architectural, histochemical & metabolic adaptations to exercise in CMT patients are the potential areas to investigate from a future research perspective to further enhance our understanding regarding the role of exercise and rehabilitation in CMT.

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Review Summary of articles on the effect of different training modalities on Charcot-Marie-Tooth disease

S. No	**Study (Author, year, & place)**	**Purpose**	**Participant**		**Age (yrs) Mean/ Range**	**Study design**	**Type of training**	**Intervention design (RCT) Outcome measures (CS)**	**Intervention / Outcome measure length**	**Results/ Findings**	**Conclusion**
			M	**F**							
1.	Burns J et al (2017) (1) New South Wales, Australia	Safety & efficacy of RT in CMT D patients	30	30	6-17	RCT	RT	Exercise group: RT (50%-70% of 1RM) Sham group: Exercise cuff training	6 months (3d/wk)	Dorsiflexion strength difference b/w groups (0 at 6 months; 0.3 at 12 months; 0.6 at 24 months	Attenuate dorsiflexion weakness, no exertion

2.	Chetlin RD et al (2004) (2) Hamilton, ON, Canada	Effect of RT on strength, body comp & ADL in CMDT patients	09	11	45.2	RCT	RT	Phase 1 (W1-4), Phase II (W5-8), Phase III (W9-12): Each Phase: (W1:4 rep, W2:6 rep, W3: 8 rep, & W4: 10 rep	12 weeks (3d/wk)	Training volume & strength showed no gender differences (p>0.05). ADLs improved after training with no gender differences	RT improved strength & ADLs equally in both men & women
3.	Eline Lindeman et al (1995) (3)Limberg, Netherland	Effect of RT on improving impairment, disability & handicap in CMTD patients	13	15	Training: 35 Control: 38	RCT	RT	W1-8: 60% of 1RM (25x3; Inter-set rest: 1 min), W9-16: 70% of 1RM (15x3; Inter-set rest: 1 min), W17-24: 80% of 1RM, (10x3; Inter-set rest: 1 min)	24 weeks (3d/wk)	Significant increase in isokinetic knee torque extension & walking distance after training	RT caused moderate increase in strength & leg-related functional performance in HMSN patients
4.	Knak KL et al (2017) (4) Copenhagen, Denmark.	Effect of aerobic anti-gravity exercise in CMTD (1A	03	02	50-64	RCT	ET	Each session: 30 min (5 min warm-up +25 min 70%-80% of HR_{max}) on anti-gravity	10 weeks (3d/wk)	Significant difference b/w baseline, pre-test, mid-test, & post-test for BBS &	Positive change in balance & improvement in walking capacity

		& X) patients						treadmill		PST, 6MWT increased throughout	
5.	El Mhandi L et al (2011) (5) Saint-Etienne, France	Effect of ITE on HRV in CMTD patients	08	00	33	RCT	ET	Each session: 45 min (5 min warm-up + Six 5-min Ex bouts: 4 min (40% P_{max}) + (alternate 1 min 80% P_{max})	12 W (S) + 12 W (NS) = 24 wks (3d/wk)	After ITE, time & frequency domain indices improved significantly (+8% mean R–R interval, +95% pNN50), 52% reduction in low/high-frequency ratio)	ITE enhances parasympathetic activity in CMT patients which improves HRV
6.	Kennedy RA et al (2019) (6) Victoria, Australia	To compare PA of CMTD children with controls & investigate it's association with disability & functional ambulation	50 (M+F)		12.5	CS	PA	Assessment of a) Patient characteristics b) Functional ambulation Physical activity Questionnaire-Children	Single outpatient assessment: Paediatric neurology clinic	Children with CMT are less active, reduced ambulatory capacity with 6MWT PA is'-' correlated with disability	CMT decreases PA which worsens CMTD progression with time
7.	Ramdharry	To compa	24	16	46	CS	PA	Assessment of	Single assess	Less number	CMTD patients

	GM et al (2017) (7) London, UK	re PA & EE of CMTD patients with controls						1. PA: Activity tracker 2. Clinical parameters: Weight. Height, Disease Severity	ment: Lab or Hospital	of total steps in CMTD however their sedentary bouts are shorter, No difference in EE	engage more in activities / movement NOT related to walking
8.	Anens E et al (2015) (8) Uppsala, Sweden	To explore facilitators & barriers to PA & it's correlation with CMTD	24	20	59,5	CS cohort survey	PA	Self-reported Survey outcomes: PA, fatigue, activity limitation, self-efficacy for PA & fall, social support, enjoyment of PA	Single survey	Barriers of PA: fatigue, poor balance, muscle weakness, and pain Facilitators of PA: self-efficacy for PA, activity assisted devices,	Personal factors e.g. self-efficacy & motivation are key in regulators of PA behaviour
9.	Ramdharry GM et al (2012) London, UK (24)	To compare differences in clinical presentation & gait function b/w CMDT patients (with & without AFO)	17	15	CMDT (with AFO) = 43.8 CMDT (without AFO) = 43.5	CS	Orthoses	Assessment of 1. Gait function 2. Disease severity, lower limb muscle strength, sensory impairment, fatigue severity perceived walking ability	Single assessment	CMDT (with AFO) walked slower, had greater disease severity, weaker leg muscles & perceived greater walking difficulty	CMDT (with AFO) were severely affected, had slower maximum walking speed, worse perceived walking ability.
10	Rose KJ et	Does 4W	14	16	Training:	RCT	Orthoses	W1-4: Serial	8 weeks	Night cast	4W night

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.	al (2010) (18), Sydney, Australia	casting + 4W stretching improve ankle dorsiflexion, mobility & balance			10 Control: 11			night casting (fiberglass, below knee flexed at 90°), W5-8: Weight bearing stretching of gastrocnemius & soleus		(after 4 W) increased ankle dorsiflexion 4° & stretching (next 4W) maintained 3° more than control group	cast improved ankle dorsiflexion range but after 8W this difference is NOT significant as compared to control

CMTD: Charcot Marie Tooth Disease; RT: Resistance training, ET: Endurance training, PA: Physical Activity, RCT: Randomised Control Trial, Ex: Exercise, ADL: Activities of Daily living, W: Week, ITE: Interval training exercise, HRV: Heart Rate Variability, S: Supervised, NS: Non-supervised; P_{max}: maximal aerobic power, BBS: Berg balance Scale, PST: Postural Stability test, 6MWT: Six minute walk test, CS: Cross sectional, EE: Energy expenditure, AFO: Ankle foot orthoses