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Gait in children and adolescents with Charcot-Marie-Tooth disease: a systematic review.

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Abstract

Symptoms of Charcot-Marie-Tooth disease (CMT) typically arise in childhood or adolescence with gait difficulty most common. A systematic review was conducted to synthesize, review and characterise gait in pediatric CMT. Health related electronic databases were reviewed with search terms related to CMT and gait. Of 454 articles, ten articles describing seven studies met eligibility criteria; samples ranged from 1-81, included mixed CMT subtypes and had a participant mean age of 13 years. Assessments included a variety of methods to examine only barefoot gait. Heterogeneity of gait patterns was noted. Children and adolescents with CMT walked slower, most likely due to shorter stride length. Common kinematic and kinetic abnormalities included significant foot drop during swing, reduced calf muscle power and proximal compensatory mechanisms in the lower limb. Little data was found to inform typical functional gait characteristics or change over time. Of note, barefoot assessment does not reflect function in everyday life where footwear is commonly worn. With limited existing literature, future studies of gait in pediatric CMT need to evaluate the influence of diagnostic subtypes and disease progression; the effect of factors such as footwear and the environment; and to explore changes in gait and function throughout childhood and adolescence.

Key words

Charcot-Marie-Tooth disease, gait, walking, pediatric, systematic review.

Introduction

Charcot-Marie-Tooth disease (CMT) is one of the most common neuromuscular diseases with an incidence of 1 in 2,500, typically diagnosed in childhood or adolescence and associated with life-long disability *(Pareyson and Marchesi, 2009; Jani-Acsadi et al., 2015*). Charcot-Marie-Tooth disease results from mutations in multiple causative genes giving rise to a wide spectrum of clinical phenotypes (*Rossor et al., 2013*). Individuals with CMT report activity limitations including walking difficulties ranging from 17% in early childhood to 57% in adolescence (*Garcia et al., 1998*). Relatively few studies have investigated gait and functional ambulation in children with CMT (*Burns et al., 2009c; Ferrarin et al., 2012; Ounpuu et al., 2013*). Children and adolescents report impaired balance leading to frequent trips and falls, reduced walking endurance and difficulty running and jumping (*Scheffers et al., 2012*). Clinical phenotype and disease progression is variable, with little pediatric longitudinal data available to indicate typical changes in gait and function over time. Knowledge of the nature of gait abnormalities in CMT is needed by pediatric clinicians to develop targeted treatment and management options including education. Currently there are no evidence based clinical guidelines in relation to gait and functional ambulation in pediatric CMT.

The aim of this systematic review is to identify, review and synthesize the evidence characterising gait in children and adolescents with CMT. The findings will summarise what is known about gait, indicate knowledge gaps and outline where

further research is required to assist healthcare clinicians working with children and adolescents with CMT and their families.

Methods

Search strategy

In accordance with the principles of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, the search strategy focussed on retrieval of publications indexed in health-related electronic databases (*Moyer et al., 2011*). The databases selected were Medline (1946 to August 14th, 2015), Embase (1947 to August 14th, 2015), CINAHL (1981 to August 14th, 2015) and SPORTSDiscus (1985 to August 14th, 2015). Search terms were customised to each database. Supplementary Table 1 provides an example of the Medline search strategy.

The initial search was conducted by one reviewer (RK) and, following removal of duplicates, articles were screened for eligibility by two independent reviewers (JM and RK). Eligibility criteria included: a diagnosis of Charcot-Marie-Tooth disease (CMT) or hereditary motor and sensory neuropathy (HMSN); a primary study reporting gait data; at least 50% of the participants aged ≤18 years; English language; full-text reports; and human studies only. Initial screening examined titles and abstracts, with full texts obtained when necessary.

Data extraction and quality review

A standardised data extraction form was developed to capture key study details. It was initially piloted on two articles by RK and KC and then finalised. Details extracted included study design, participant recruitment source, sample demographic

and clinical characteristics, gait measurement systems and test conditions, gait data type and statistical analysis methods. Detailed gait results were extracted by one reviewer (RK) and confirmed by a second (KC). Where multiple time point data were available, only baseline data was extracted. Articles from the same author groups were closely examined to identify multiple descriptions of the same data sets.

Study methodological quality was assessed with a modified version of the Quality Index checklist (QI) (*Downs and Black, 1998*). The original QI was reviewed and items not within the scope of the current review relating to interventions and longitudinal data were removed. Thirteen items remained with a total possible score out of 14. If disagreement occurred between the independent scoring of QI items, the third reviewer (JM) adjudicated. For ease of comparison QI scores were converted to a percentage of the total score.

Results

The search yielded an initial 454 articles (Fig. 1), with a final yield of ten eligible articles (*Chan et al., 2007; Newman et al., 2007; Burns et al., 2009a; Burns et al., 2009b; Burns et al., 2009c; Rose et al., 2010; Blyton et al., 2011; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*).

- Insert Figure 1 -

Study and participant characteristics

Preliminary review of the ten articles identified studies and samples that were described in more than one article, with data from seven independent studies identified. Notably, two articles appeared to describe gait of one sample (*Ferrarin et al., 2012; Ferrarin et al., 2013*) and another three described a sample from a clinical trial of ascorbic acid (*Burns et al., 2009a; Burns et al., 2009c; Blyton et al., 2011*)[1]. Table 1 lists study characteristics of included articles.

Study designs included two randomised control trials (RCT), cross-sectional, case-control and longitudinal observational studies and a single case study. Both RCTs were intervention studies with CMT placebo groups and recorded gait characteristics as secondary outcome measures (*Burns et al., 2009a; Rose et al., 2010*). Four studies had a primary aim of describing gait characteristics; all compared findings to their respective gait laboratory reference group of typically developing (TD) controls with statistical analysis (*Chan et al., 2007; Newman et al.,*

[1] Correspondence with the lead author confirmed that two articles, Blyton et al, 2011 and Burns et al, 2009c, were post hoc analyses of baseline data from the Ascorbic acid study, Burns et al, 2009a.

2007; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013). Two of these studies sub-grouped data according to gait patterns (*Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*). One further article compared gait data from the ascorbic acid trial (*Burns et al., 2009a*) to published normative values and grouped data into age bands across childhood and adolescence but did not provide statistical analysis (*Burns et al., 2009c*).

Sample numbers varied widely, ranging from one to 81 with a total of 191 participants across seven studies. Participant age ranged from 2-52 years with a mean of the reported ages of 13 years. Two articles included participants aged over 18 years (*Newman et al., 2007; Rose et al., 2010*) with no individual gait data available for sub analysis. These articles were retained as the mean age was 14 years or less. Studies included a mix of CMT subtypes with two of the seven studies assessing children with CMT1A only (*Burns et al., 2009a; Ferrarin et al., 2012*). Age at time of diagnosis was noted in three studies and ranged from 4-14 years (*Newman et al., 2007; Ferrarin et al., 2012; Ounpuu et al., 2013*).

Notably, eligibility criteria varied across studies and were poorly defined in some studies. Only three studies reported exclusion of participants whose gait might be affected by diseases other than CMT, lower limb injury or surgery (*Burns et al., 2009a; Rose et al., 2010; Ferrarin et al., 2012*). One study excluded those unable to walk unaided barefoot (*Ferrarin et al., 2012*).

Participants in all studies were independently ambulant during gait testing. A description of the ability of participants to walk in the community or beyond short

distances was not commonly reported, with only three studies describing limitations (*Newman et al., 2007; Burns et al., 2009b; Burns et al., 2009c*). Functional limitations included reduced endurance in up to 25% of participants (*Newman et al., 2007; Burns et al., 2009b*), reduced balance (*Burns et al., 2009c*) and a high falls incidence in 47% of children (*Burns et al., 2009c*). A single study reported inclusion of a child with the severe phenotype Dejerine-Sottas disease (DS) who used a power wheelchair for longer distances (*Rose et al., 2010*). Of note, no study utilised a standardised assessment tool to describe functional ambulatory ability.

Foot and ankle impairments were reported in six of the seven studies and included reduced range of motion (*Burns et al., 2009c; Rose et al., 2010*; *Ounpuu et al., 2013)*, reduced strength (*Burns et al., 2009b; Burns et al., 2009c; Ferrarin et al., 2012; Ounpuu et al., 2013*) and ankle instability/recurrent sprains (*Newman et al., 2007; Burns et al., 2009b; Burns et al., 2009c;*). All studies noted the presence of foot deformity in some participants. Most studies did not report whether the participants used orthotics in daily functional ambulation, with only a single study reporting the use of in shoe orthotics (*Burns et al., 2009b*).

Gait data

Gait was measured with a diverse range of methods and measurement systems (Table 1). Six studies reported testing at self-selected preferred walking speed, with gait testing conditions likely to be barefoot, either as stated or assumed from methodology. Reporting of footwear condition varied with five studies explicitly describing barefoot testing (*Newman et al., 2007; Burns et al., 2009a; Burns et al.,*

2009b; Ferrarin et al., 2012; Ounpuu et al., 2013) and no reports of gait tested in footwear or orthotic-footwear combinations.

Spatio-temporal gait data

Nine of the ten articles reported spatio-temporal gait data (Table 2). Speed was reported in all, cadence in seven and stride length in six. Despite use of detailed measurement systems, additional measures were not uniformly reported, such as step time, step length and base of support width. Of note, only three articles presented speed and stride length data normalised to body anthropometrics, an important consideration given the wide range of age groups with subsequent variation in participant height and leg length (*Newman et al., 2007; Ferrarin et al., 2012; Ferrarin et al., 2013*). Furthermore, in two articles the TD cohort walked at speeds matched to the CMT groups to allow for kinematic and kinetic comparison (*Ferrarin et al., 2012; Ferrarin et al., 2013*).

Speed

Self-selected gait speed was generally slower in CMT groups compared to their TD peers, ranging widely from 0.50 m/sec to 1.25 m/sec. Only three articles provided a between-group statistical analysis of speed of CMT and TD or reference cohorts. Subgroup analysis in two articles found that more severely affected children were significantly slower. Ounpuu and colleagues (2013) found the “typical” and “foot drop” subgroups walked significantly slower, in contrast to the “toe walkers” subgroup (*Ounpuu et al., 2013*). Similarly, the most severely impaired foot drop and push-off deficit (FD&POD) subgroup in Ferrarin and colleagues’ study walked

significantly slower than TD controls, despite group speed matching (*Ferrarin et al., 2012*).

To gain further insight into speed differences, data from five studies (*Newman et al., 2007; Burns et al., 2009a; Rose et al., 2010; Ferrarin et al., 2013; Ounpuu et al., 2013*) are presented in Figure 2, relative to two TD cohorts (*Newman et al., 2007; Ounpuu et al., 2013*) and gait speed data from a sample of 62 12-year-old TD children (*Lythgo et al., 2009*). To avoid duplicate reporting, only the initial study of the ascorbic acid cohort was included (*Burns et al., 2009a*). Normalised data (*Ferrarin et al., 2012*) was not included nor the single case study (*Burns et al., 2009b*). The wider confidence intervals (CI) in the CMT data indicate greater variability in speed and reflect the relatively small sample sizes. Of note is the slower outlying data from both CMT groups in the study by Rose and colleagues which included mixed subtypes and a child with DS (*Rose et al., 2010*). Variability in average speed of the CMT cohorts is apparent, with the overlapping CI in four of the five studies suggesting little difference between gait speeds (*Newman et al., 2007; Burns et al., 2009a; Ferrarin et al., 2013; Ounpuu et al., 2013*). In contrast, TD groups' speeds are relatively homogeneous with narrow CI in the Lythgo data due to larger sample size. The CI of only one of the nine CMT groups (*Burns et al., 2009a*) narrowly overlaps Lythgo's TD data indicating gait speed of most cohorts of children with CMT is slower than TD.

- Insert Figure 2 -

Stride length

Stride length is the distance measured from initial contact of one foot to the subsequent initial contact of the same foot. Only two articles provided statistical comparison of CMT stride length to TD children; both were speed matched trials hence limiting interpretation (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Normalised stride length was significantly reduced in only the most severely impaired subgroup of children with CMT (mean difference 0.10 m, ES=1.0) (*Ferrarin et al., 2013*).

Cadence

Cadence, the number of steps per minute, was not significantly different between children with CMT and TD (*Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*), however, comparison to speed matched trials in two of these articles again limits interpretation (*Ferrarin et al., 2012; Ferrarin et al., 2013*).

Step time, step length and base of support width

Step time is measured as the time between initial contact of one foot and initial contact of the next. Step length is the distance from initial contact of one foot to initial contact of the opposite foot. Base of support width (BOS) reflects the distance from the heel centre of one footprint to the line of progression formed by two footprints of the opposite foot. Only one study suggested children with CMT walk with comparable step time, reduced step length and wider BOS compared to age-equivalent norms but provided no statistical analysis (*Burns et al., 2009c*).

Kinematic and kinetic gait data

Kinematic and kinetic data with reference to TD databases were reported in four articles describing three studies (Table 3) (*Newman et al., 2007; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu, et al., 2013*). As previously noted, two articles speed-matched the TD group to examine alterations independent of speed (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Although kinematic and kinetic differences were evident at all levels (hip, knee and ankle); not all were found to be statistically significant. Three articles subdivided their cohorts based on gait patterns (*Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*). Ounpuu et al, (2013) grouped their cohort based on peak ankle dorsiflexion in terminal stance into “toe-walker” (TW), “typical” or “foot drop” (FD) sub-groups. Ferrarin et al, (2012; 2013) identified gait patterns through cluster analysis as “pseudo-normal/normal looking” (PN/NL), “foot drop” (FD) and “foot drop and push-off deficit” (FD&POD).

Statistically significant kinematic differences were found at all joints, with the majority at the ankle. ‘Foot drop’ or reduced peak dorsiflexion in swing phase was reported in all studies. Notably, all studies found abnormal ankle kinetics with reduced power generation or reduced positive work in stance (*Newman et al., 2007; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*). Only two of four articles found significant differences in gait patterns at the hip and knee (*Newman et al., 2007; Ferrarin et al., 2012*). Key differences included greater range of hip motion and increased hip flexion (*Ferrarin et al., 2012*), hip abduction and external rotation

(*Newman et al., 2007*), and greater peak knee extension in stance (*Newman et al., 2007*).

Pedobarograph data

Pedobarography measures pressure distribution where the foot makes contact with the underlying surface. Pedobarograph data prior and post corrective foot surgery for pes cavus was reported relative to a laboratory reference group (*Chan et al., 2007*). Pre-surgery foot pressure measurements were significantly increased over the lateral mid foot (mean 35.2%/body weight, $p<0.001$) reflecting the high medial arched deformity. Forefoot pressure both laterally and medially was significantly reduced (*Chan et al., 2007*) indicating reduced push-off.

Functional gait data – Six minute walk test (6MWT)

Functional ambulatory performance measured by the 6MWT varied widely in four articles from two studies by Burns and colleagues (*Burns et al., 2009a; Burns et al., 2009b; Burns et al., 2009c; Blyton et al., 2011*). Distance (6MWD) ranged markedly from 110 to 710 metres with the largest sample of 65 children walking an average of 520 metres (*Burns et al., 2009a*). Sub-division into cross-sectional age groupings and comparison to published norms indicated that 6MWD increased throughout early to middle childhood, however appeared to decline in the adolescent group.

Study quality

Study quality is detailed in Supplementary Table 2. Study quality varied widely from as low as 6/14 (43%) to 14/14 (100%). Key methodological strengths included well described patient populations in 8 out of 10 articles and use of valid and reliable outcome measures. Weaknesses included insufficient representativeness of study populations, with generalizability of study findings excellent in only three articles describing well-defined populations and participant selection (*Burns et al., 2009a; Rose et al., 2010; Blyton et al., 2011*). Confounders such as other factors impairing gait were not reported in four articles (*Chan et al., 2007; Newman et al., 2007; Burns et al., 2009b; Ounpuu et al., 2013*). Heterogeneity of study methodologies, samples and variability in the available data precluded item pooling for meta-analysis.

Discussion

More than 50% of children and adolescents with CMT report difficulty walking, yet very few studies have investigated gait deviations in this population. The ten articles in this review reported on findings from just seven studies. This review found that children with CMT walk more slowly than their TD peers with foot drop in swing, reduced calf power at push off and associated compensatory strategies of hip flexion, external rotation and abduction in swing indicative of a high stepping gait pattern. Few studies described functional ambulation and only one study reported gait changes over time.

Slower walking speed may be due to alterations in stride length and/or cadence. The only statistical comparison of stride length data occurred in studies that speed-matched trials from TD children (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Inspection of the non-normalised stride length data across studies suggests stride length is shorter than reported stride length for TD 12-year-olds whilst cadence is similar, thus accounting for the slower speed (*Burns et al., 2009c; Lythgo et al., 2009*). Notably, stride length was not normalised in all studies, which is an important consideration given the wide age range and height/leg length differences of the participants.

Abnormal motion at the ankle contributes to gait dysfunction in children with CMT. The high incidence of reported trips and falls are the likely consequence of reduced dorsiflexion in swing and increased plantar flexion at initial contact, more commonly referred to as “foot drop”. Typical compensatory strategies of hip flexion,

external rotation and abduction are adopted to clear the foot in swing. Pedobarograph data demonstrates reduced forefoot pressures indicative of ineffectual push-off (*Chan et al., 2007*). Reduced calf power generation at push off as shown in kinetic studies contributes to shorter stride length and slower gait speed. Additionally, of particular interest, no studies included complex foot models such as the Oxford foot model (*Stebbins et al., 2006*) to provide more accurate and complete description of ankle/foot biomechanics. It is recommended that future biomechanical studies should include detailed foot modelling as foot posture is a hallmark feature of CMT.

Heterogeneity of disease severity both between sub-types and within sub-types is well documented in CMT (*Pareyson and Marchesi, 2009*). The large variation in gait characteristics in this review likely reflects the diversity of diagnostic sub-types and wide participant age range. The effect of CMT on gait speed is large with effect sizes ranging from 1.5 to 2.3 in the groups that walked more slowly. Insight into the association between disease severity and speed is provided by clinical subgroup analysis, finding that children with foot drop walked slowest (ES=2.3) (*Ounpuu et al., 2013*). Examination of the variation in cross-sectional speed data (Fig. 2) relative to sub-types provides further potential insights. The two studies including only participants with the typically milder phenotype CMT1A (*Burns et al., 2009a; Ferrarin et al., 2013*) reported the fastest average gait speed. No studies compared or analysed subtypes separately. The development of CMTPedS as a valid and a reliable assessment of disease severity (*Burns et al., 2012*), together with

advances in genetic diagnosis of CMT subtypes, warrants future research to investigate links between disease severity, subtype and gait dysfunction in children with CMT.

Consideration of gait beyond the context of an unobstructed level indoor gait laboratory environment is needed, as these gait tests are not reflective of day to day life for children and adolescents with CMT in their home and community settings. The speed and distance requirements of school and community walking have not been clearly defined for children. In adults, speed and distance requirements for functional community ambulation range up to 1.32 m/sec and 677 metres, respectively (*Salbach et al., 2014*). Functional adult walking speed is estimated to be 80 cm/sec with speeds below this threshold reflecting limited community ambulation (*Perry et al., 1995*). Data within this review suggests that many children may have difficulty walking at speeds required in the community, with some walking 0.20-0.30 m/sec slower (*Rose et al., 2010*). Similarly, many children may have difficulty walking the distances required within their local communities, with 6MWD ranging from 110-710 metres (*Burns et al., 2009a*). Slower gait speed is a potential barrier to participation and the ability to keep up with TD peers in school and community environments. There are no published minimally clinically important differences (MCID) values for gait speed in children, however, in older adults MCID range from 0.05 m/sec to 0.13 m/sec (*Perera et al., 2006*). The mean speeds of the CMT cohorts are 0.10 – 0.30 m/sec slower than the TD cohorts or TD reference group

(*Lythgo et al., 2009*). This exceeds the adult MCID threshold, suggesting slower walking speeds may impact daily life of children and adolescents with CMT.

In other populations with gait dysfunction researchers have developed functional gait classification systems or scales to more accurately describe functional ambulation in broader environmental contexts. The Functional Mobility Scale (FMS) (*Graham et al., 2004*) is one example commonly used for children with cerebral palsy. The FMS assesses mobility over 5, 50 and 500 metres taking into consideration the different environmental contexts of home, school and community. The FMS also accounts for uneven surfaces and stairs. No such functional ambulatory assessment has been reported in the CMT pediatric gait literature but consideration of these factors is equally important to this population, with appropriate selection of responsive tools needed.

It is noteworthy that there were no studies of children walking in footwear identified in this review. Whilst assessment of barefoot gait is usual in laboratory settings and provides insight into primary biomechanical dysfunction, this does not readily translate to “real world” function of walking in school and community settings. Children and adolescents with CMT rarely walk barefoot beyond the indoor home environment, typically wearing footwear outdoors. Studies in TD children demonstrate faster gait with a longer stride length when wearing shoes compared to barefoot gait (*Lythgo et al., 2009; Wegener et al., 2011*). Importantly, some people with CMT wear foot orthotics for support of foot and ankle weakness and/or biomechanical alignment. Further studies are needed to understand gait in the

functional context of footwear, either with or without orthotics, to more closely reflect school and community function.

A number of limitations warrant consideration in this review. Relatively few studies, small cohort numbers and the lack of statistical analysis in nearly half of the studies limit the findings. Speed-matching in two articles alters interpretation of the spatio-temporal data (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Studies varied in quality in terms of control of extraneous or confounding factors, and uncertain sample generalisability. Of additional note, no study reported the presence of hip dysplasia, which has a reported incidence of up to 8.1% in CMT (*Walker et al., 1994*) and may significantly influence gait.

This systematic review of cross-sectional studies provided limited insight into progression of CMT over time, or the influence of age. It is noteworthy that only a single small study examined longitudinal changes in gait during childhood (*Ferrarin et al., 2013*), finding a small non-significant decline over an 18 month period. In comparison, several studies span adulthood, some of which include adolescents (*Berciano et al., 2006; Shy et al., 2008; Verhamme et al., 2009; Milhe De Bovis et al., 2014; Pelayo-Negro et al., 2014*). As CMT typically emerges during childhood, and is known to be progressive more longitudinal pediatric studies are needed. Future research should include gait assessment in footwear and usual orthotics, in conjunction with evaluations of gait in a functional environmental context to provide important insights into real-life performance of children and adolescents with CMT.

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Conflict of interest statement

The authors have no conflicts of interest.

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Figure legend

Figure 1 Search history and selection flow diagram.

Figure 2 Average gait speed from selected CMT studies in relation to typically developing controls.

Table legend

Table 1 Characteristics of included articles.

Table 2 Spatio-temporal gait data from included articles reported as mean [SD].

Table 3 Key statistical analysis of lower limb kinematic and kinetic gait data of children with CMT relative to typically developing children.

Supplementary table legend

Supplementary table 1: Example of search strategy.

Supplementary table 2: Quality Index scores.

Gait in children and adolescents with Charcot-Marie-Tooth disease: a systematic review.

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Abstract

Symptoms of Charcot-Marie-Tooth disease (CMT) typically arise in childhood or adolescence with gait difficulty most common. A systematic review was conducted to synthesize, review and characterise gait in pediatric CMT. Health related electronic databases were reviewed with search terms related to CMT and gait. Of 454 articles, ten articles describing seven studies met eligibility criteria; samples ranged from 1-81, included mixed CMT subtypes and had a participant mean age of 13 years. Assessments included a variety of methods to examine only barefoot gait. Heterogeneity of gait patterns was noted. Children and adolescents with CMT walked slower, most likely due to shorter stride length. Common kinematic and kinetic abnormalities included significant foot drop during swing, reduced calf muscle power and proximal compensatory mechanisms in the lower limb. Little data was found to inform typical functional gait characteristics or change over time. Of note, barefoot assessment does not reflect function in everyday life where footwear is commonly worn. With limited existing literature, future studies of gait in pediatric CMT need to evaluate the influence of diagnostic subtypes and disease progression; the effect of factors such as footwear and the environment; and to explore changes in gait and function throughout childhood and adolescence.

Key words

Charcot-Marie-Tooth disease, gait, walking, pediatric, systematic review.

Introduction

Charcot-Marie-Tooth disease (CMT) is one of the most common neuromuscular diseases with an incidence of 1 in 2,500, typically diagnosed in childhood or adolescence and associated with life-long disability *(Pareyson and Marchesi, 2009; Jani-Acsadi et al., 2015*). Charcot-Marie-Tooth disease results from mutations in multiple causative genes giving rise to a wide spectrum of clinical phenotypes (*Rossor et al., 2013*). Individuals with CMT report activity limitations including walking difficulties ranging from 17% in early childhood to 57% in adolescence (*Garcia et al., 1998*). Relatively few studies have investigated gait and functional ambulation in children with CMT (*Burns et al., 2009c; Ferrarin et al., 2012; Ounpuu et al., 2013*). Children and adolescents report impaired balance leading to frequent trips and falls, reduced walking endurance and difficulty running and jumping (*Scheffers et al., 2012*). Clinical phenotype and disease progression is variable, with little pediatric longitudinal data available to indicate typical changes in gait and function over time. Knowledge of the nature of gait abnormalities in CMT is needed by pediatric clinicians to develop targeted treatment and management options including education. Currently there are no evidence based clinical guidelines in relation to gait and functional ambulation in pediatric CMT.

The aim of this systematic review is to identify, review and synthesize the evidence characterising gait in children and adolescents with CMT. The findings will summarise what is known about gait, indicate knowledge gaps and outline where further research is required to assist healthcare clinicians working with children and adolescents with CMT and their families.

Methods

Search strategy

In accordance with the principles of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, the search strategy focussed on retrieval of publications indexed in health-related electronic databases (*Moyer et al., 2011*). The databases selected were Medline (1946 to August 14th, 2015), Embase (1947 to August 14th, 2015), CINAHL (1981 to August 14th, 2015) and SPORTSDiscus (1985 to August 14th, 2015). Search terms were customised to each database. Supplementary Table 1 provides an example of the Medline search strategy.

The initial search was conducted by one reviewer (RK) and, following removal of duplicates, articles were screened for eligibility by two independent reviewers (JM and RK). Eligibility criteria included: a diagnosis of Charcot-Marie-Tooth disease (CMT) or hereditary motor and sensory neuropathy (HMSN); a primary study reporting gait data; at least 50% of the participants aged ≤18 years; English language; full-text reports; and human studies only. Initial screening examined titles and abstracts, with full texts obtained when necessary.

Data extraction and quality review

A standardised data extraction form was developed to capture key study details. It was initially piloted on two articles by RK and KC and then finalised. Details extracted included study design, participant recruitment source, sample demographic and clinical characteristics, gait measurement systems and test conditions, gait data type and statistical analysis methods. Detailed gait results were extracted by one reviewer (RK) and confirmed by a second (KC). Where multiple time point data were

available, only baseline data was extracted. Articles from the same author groups were closely examined to identify multiple descriptions of the same data sets.

Study methodological quality was assessed with a modified version of the Quality Index checklist (QI) (*Downs and Black, 1998*). The original QI was reviewed and items not within the scope of the current review relating to interventions and longitudinal data were removed. Thirteen items remained with a total possible score out of 14. If disagreement occurred between the independent scoring of QI items, the third reviewer (JM) adjudicated. For ease of comparison QI scores were converted to a percentage of the total score.

Results

The search yielded an initial 454 articles (Fig. 1), with a final yield of ten eligible articles (*Chan et al., 2007; Newman et al., 2007; Burns et al., 2009a; Burns et al., 2009b; Burns et al., 2009c; Rose et al., 2010; Blyton et al., 2011; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*).

- Insert Figure 1 -

Study and participant characteristics

Preliminary review of the ten articles identified studies and samples that were described in more than one article, with data from seven independent studies identified. Notably, two articles appeared to describe gait of one sample (*Ferrarin et al., 2012; Ferrarin et al., 2013*) and another three described a sample from a clinical trial of ascorbic acid (*Burns et al., 2009a; Burns et al., 2009c; Blyton et al., 2011*)[1]. Table 1 lists study characteristics of included articles.

Study designs included two randomised control trials (RCT), cross-sectional, case-control and longitudinal observational studies and a single case study. Both RCTs were intervention studies with CMT placebo groups and recorded gait characteristics as secondary outcome measures (*Burns et al., 2009a; Rose et al., 2010*). Four studies had a primary aim of describing gait characteristics; all compared findings to their respective gait laboratory reference group of typically developing (TD) controls with statistical analysis (*Chan et al., 2007; Newman et al., 2007; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*). Two of these studies sub-grouped data according to gait patterns (*Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*). One further article compared gait data from the

[1] Correspondence with the lead author confirmed that two articles, Blyton et al, 2011 and Burns et al, 2009c, were post hoc analyses of baseline data from the Ascorbic acid study, Burns et al, 2009a.

ascorbic acid trial (*Burns et al., 2009a*) to published normative values and grouped data into age bands across childhood and adolescence but did not provide statistical analysis (*Burns et al., 2009c*).

Sample numbers varied widely, ranging from one to 81 with a total of 191 participants across seven studies. Participant age ranged from 2-52 years with a mean of the reported ages of 13 years. Two articles included participants aged over 18 years (*Newman et al., 2007; Rose et al., 2010*) with no individual gait data available for sub analysis. These articles were retained as the mean age was 14 years or less. Studies included a mix of CMT subtypes with two of the seven studies assessing children with CMT1A only (*Burns et al., 2009a; Ferrarin et al., 2012*). Age at time of diagnosis was noted in three studies and ranged from 4-14 years (*Newman et al., 2007; Ferrarin et al., 2012; Ounpuu et al., 2013*).

Notably, eligibility criteria varied across studies and were poorly defined in some studies. Only three studies reported exclusion of participants whose gait might be affected by diseases other than CMT, lower limb injury or surgery (*Burns et al., 2009a; Rose et al., 2010; Ferrarin et al., 2012*). One study excluded those unable to walk unaided barefoot (*Ferrarin et al., 2012*).

Participants in all studies were independently ambulant during gait testing. A description of the ability of participants to walk in the community or beyond short distances was not commonly reported, with only three studies describing limitations (*Newman et al., 2007; Burns et al., 2009b; Burns et al., 2009c*). Functional limitations included reduced endurance in up to 25% of participants (*Newman et al., 2007; Burns et al., 2009b*), reduced balance (*Burns et al., 2009c*) and a high falls incidence in 47% of children (*Burns et al., 2009c*). A single study reported inclusion of a child

with the severe phenotype Dejerine-Sottas disease (DS) who used a power wheelchair for longer distances (*Rose et al., 2010*). Of note, no study utilised a standardised assessment tool to describe functional ambulatory ability.

Foot and ankle impairments were reported in six of the seven studies and included reduced range of motion (*Burns et al., 2009c; Rose et al., 2010*; *Ounpuu et al., 2013)*, reduced strength (*Burns et al., 2009b; Burns et al., 2009c; Ferrarin et al., 2012; Ounpuu et al., 2013*) and ankle instability/recurrent sprains (*Newman et al., 2007; Burns et al., 2009b; Burns et al., 2009c;*). All studies noted the presence of foot deformity in some participants. Most studies did not report whether the participants used orthotics in daily functional ambulation, with only a single study reporting the use of in shoe orthotics (*Burns et al., 2009b*).

Gait data

Gait was measured with a diverse range of methods and measurement systems (Table 1). Six studies reported testing at self-selected preferred walking speed, with gait testing conditions likely to be barefoot, either as stated or assumed from methodology. Reporting of footwear condition varied with five studies explicitly describing barefoot testing (*Newman et al., 2007; Burns et al., 2009a; Burns et al., 2009b; Ferrarin et al., 2012; Ounpuu et al., 2013*) and no reports of gait tested in footwear or orthotic-footwear combinations.

Spatio-temporal gait data

Nine of the ten articles reported spatio-temporal gait data (Table 2). Speed was reported in all, cadence in seven and stride length in six. Despite use of detailed measurement systems, additional measures were not uniformly reported, such as step time, step length and base of support width. Of note, only three articles

presented speed and stride length data normalised to body anthropometrics, an important consideration given the wide range of age groups with subsequent variation in participant height and leg length (*Newman et al., 2007; Ferrarin et al., 2012; Ferrarin et al., 2013*). Furthermore, in two articles the TD cohort walked at speeds matched to the CMT groups to allow for kinematic and kinetic comparison (*Ferrarin et al., 2012; Ferrarin et al., 2013*).

Speed

Self-selected gait speed was generally slower in CMT groups compared to their TD peers, ranging widely from 0.50 m/sec to 1.25 m/sec. Only three articles provided a between-group statistical analysis of speed of CMT and TD or reference cohorts. Subgroup analysis in two articles found that more severely affected children were significantly slower. Ounpuu and colleagues (2013) found the “typical” and “foot drop” subgroups walked significantly slower, in contrast to the “toe walkers” subgroup (*Ounpuu et al., 2013*). Similarly, the most severely impaired foot drop and push-off deficit (FD&POD) subgroup in Ferrarin and colleagues’ study walked significantly slower than TD controls, despite group speed matching (*Ferrarin et al., 2012*).

To gain further insight into speed differences, data from five studies (*Newman et al., 2007; Burns et al., 2009a; Rose et al., 2010; Ferrarin et al., 2013; Ounpuu et al., 2013*) are presented in Figure 2, relative to two TD cohorts (*Newman et al., 2007; Ounpuu et al., 2013*) and gait speed data from a sample of 62 12-year-old TD children (*Lythgo et al., 2009*). To avoid duplicate reporting, only the initial study of the ascorbic acid cohort was included (*Burns et al., 2009a*). Normalised data (*Ferrarin et al., 2012*) was not included nor the single case study (*Burns et al., 2009b*). The wider confidence intervals (CI) in the CMT data indicate greater

variability in speed and reflect the relatively small sample sizes. Of note is the slower outlying data from both CMT groups in the study by Rose and colleagues which included mixed subtypes and a child with DS (*Rose et al., 2010*). Variability in average speed of the CMT cohorts is apparent, with the overlapping CI in four of the five studies suggesting little difference between gait speeds (*Newman et al., 2007; Burns et al., 2009a; Ferrarin et al., 2013; Ounpuu et al., 2013*). In contrast, TD groups' speeds are relatively homogeneous with narrow CI in the Lythgo data due to larger sample size. The CI of only one of the nine CMT groups (*Burns et al., 2009a*) narrowly overlaps Lythgo's TD data indicating gait speed of most cohorts of children with CMT is slower than TD.

- Insert Figure 2 -

Stride length

Stride length is the distance measured from initial contact of one foot to the subsequent initial contact of the same foot. Only two articles provided statistical comparison of CMT stride length to TD children; both were speed matched trials hence limiting interpretation (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Normalised stride length was significantly reduced in only the most severely impaired subgroup of children with CMT (mean difference 0.10 m, ES=1.0) (*Ferrarin et al., 2013*).

Cadence

Cadence, the number of steps per minute, was not significantly different between children with CMT and TD (*Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*), however, comparison to speed matched trials in two of these articles again limits interpretation (*Ferrarin et al., 2012; Ferrarin et al., 2013*).

Step time, step length and base of support width

Step time is measured as the time between initial contact of one foot and initial contact of the next. Step length is the distance from initial contact of one foot to initial contact of the opposite foot. Base of support width (BOS) reflects the distance from the heel centre of one footprint to the line of progression formed by two footprints of the opposite foot. Only one study suggested children with CMT walk with comparable step time, reduced step length and wider BOS compared to age-equivalent norms but provided no statistical analysis (*Burns et al., 2009c*).

Kinematic and kinetic gait data

Kinematic and kinetic data with reference to TD databases were reported in four articles describing three studies (Table 3) (*Newman et al., 2007; Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu, et al., 2013*). As previously noted, two articles speed-matched the TD group to examine alterations independent of speed (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Although kinematic and kinetic differences were evident at all levels (hip, knee and ankle); not all were found to be statistically significant. Three articles subdivided their cohorts based on gait patterns (*Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013*). Ounpuu et al, (2013) grouped their cohort based on peak ankle dorsiflexion in terminal stance into “toe-walker” (TW), “typical” or “foot drop” (FD) sub-groups. Ferrarin et al, (2012; 2013) identified gait patterns through cluster analysis as “pseudo-normal/normal looking” (PN/NL), “foot drop” (FD) and “foot drop and push-off deficit” (FD&POD).

Statistically significant kinematic differences were found at all joints, with the majority at the ankle. ‘Foot drop’ or reduced peak dorsiflexion in swing phase was reported in all studies. Notably, all studies found abnormal ankle kinetics with reduced power generation or reduced positive work in stance (*Newman et al., 2007;*

Ferrarin et al., 2012; Ferrarin et al., 2013; Ounpuu et al., 2013). Only two of four articles found significant differences in gait patterns at the hip and knee (*Newman et al., 2007; Ferrarin et al., 2012*). Key differences included greater range of hip motion and increased hip flexion (*Ferrarin et al., 2012*), hip abduction and external rotation (*Newman et al., 2007*), and greater peak knee extension in stance (*Newman et al., 2007*).

Pedobarograph data

Pedobarography measures pressure distribution where the foot makes contact with the underlying surface. Pedobarograph data prior and post corrective foot surgery for pes cavus was reported relative to a laboratory reference group (*Chan et al., 2007*). Pre-surgery foot pressure measurements were significantly increased over the lateral mid foot (mean 35.2%/body weight, $p<0.001$) reflecting the high medial arched deformity. Forefoot pressure both laterally and medially was significantly reduced (*Chan et al., 2007*) indicating reduced push-off.

Functional gait data – Six minute walk test (6MWT)

Functional ambulatory performance measured by the 6MWT varied widely in four articles from two studies by Burns and colleagues (*Burns et al., 2009a; Burns et al., 2009b; Burns et al., 2009c; Blyton et al., 2011*). Distance (6MWD) ranged markedly from 110 to 710 metres with the largest sample of 65 children walking an average of 520 metres (*Burns et al., 2009a*). Sub-division into cross-sectional age groupings and comparison to published norms indicated that 6MWD increased throughout early to middle childhood, however appeared to decline in the adolescent group.

Study quality

Study quality is detailed in Supplementary Table 2. Study quality varied widely from as low as 6/14 (43%) to 14/14 (100%). Key methodological strengths included well described patient populations in 8 out of 10 articles and use of valid and reliable outcome measures. Weaknesses included insufficient representativeness of study populations, with generalizability of study findings excellent in only three articles describing well-defined populations and participant selection (*Burns et al., 2009a; Rose et al., 2010; Blyton et al., 2011*). Confounders such as other factors impairing gait were not reported in four articles (*Chan et al., 2007; Newman et al., 2007; Burns et al., 2009b; Ounpuu et al., 2013*). Heterogeneity of study methodologies, samples and variability in the available data precluded item pooling for meta-analysis.

Discussion

More than 50% of children and adolescents with CMT report difficulty walking, yet very few studies have investigated gait deviations in this population. The ten articles in this review reported on findings from just seven studies. This review found that children with CMT walk more slowly than their TD peers with foot drop in swing, reduced calf power at push off and associated compensatory strategies of hip flexion, external rotation and abduction in swing indicative of a high stepping gait pattern. Few studies described functional ambulation and only one study reported gait changes over time.

Slower walking speed may be due to alterations in stride length and/or cadence. The only statistical comparison of stride length data occurred in studies that speed-matched trials from TD children (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Inspection of the non-normalised stride length data across studies suggests stride length is shorter than reported stride length for TD 12-year-olds whilst cadence is similar, thus accounting for the slower speed (*Burns et al., 2009c; Lythgo et al., 2009*). Notably, stride length was not normalised in all studies, which is an important consideration given the wide age range and height/leg length differences of the participants.

Abnormal motion at the ankle contributes to gait dysfunction in children with CMT. The high incidence of reported trips and falls are the likely consequence of reduced dorsiflexion in swing and increased plantar flexion at initial contact, more commonly referred to as “foot drop”. Typical compensatory strategies of hip flexion, external rotation and abduction are adopted to clear the foot in swing. Pedobarograph data demonstrates reduced forefoot pressures indicative of

ineffectual push-off (*Chan et al., 2007*). Reduced calf power generation at push off as shown in kinetic studies contributes to shorter stride length and slower gait speed. Additionally, of particular interest, no studies included complex foot models such as the Oxford foot model (*Stebbins et al., 2006*) to provide more accurate and complete description of ankle/foot biomechanics. It is recommended that future biomechanical studies should include detailed foot modelling as foot posture is a hallmark feature of CMT.

Heterogeneity of disease severity both between sub-types and within sub-types is well documented in CMT (*Pareyson and Marchesi, 2009*). The large variation in gait characteristics in this review likely reflects the diversity of diagnostic sub-types and wide participant age range. The effect of CMT on gait speed is large with effect sizes ranging from 1.5 to 2.3 in the groups that walked more slowly. Insight into the association between disease severity and speed is provided by clinical subgroup analysis, finding that children with foot drop walked slowest (ES=2.3) (*Ounpuu et al., 2013*). Examination of the variation in cross-sectional speed data (Fig. 2) relative to sub-types provides further potential insights. The two studies including only participants with the typically milder phenotype CMT1A (*Burns et al., 2009a; Ferrarin et al., 2013*) reported the fastest average gait speed. No studies compared or analysed subtypes separately. The development of CMTPedS as a valid and a reliable assessment of disease severity (*Burns et al., 2012*), together with advances in genetic diagnosis of CMT subtypes, warrants future research to investigate links between disease severity, subtype and gait dysfunction in children with CMT.

Consideration of gait beyond the context of an unobstructed level indoor gait laboratory environment is needed, as these gait tests are not reflective of day to day

life for children and adolescents with CMT in their home and community settings. The speed and distance requirements of school and community walking have not been clearly defined for children. In adults, speed and distance requirements for functional community ambulation range up to 1.32 m/sec and 677 metres, respectively (*Salbach et al., 2014*). Functional adult walking speed is estimated to be 80 cm/sec with speeds below this threshold reflecting limited community ambulation (*Perry et al., 1995*). Data within this review suggests that many children may have difficulty walking at speeds required in the community, with some walking 0.20-0.30 m/sec slower (*Rose et al., 2010*). Similarly, many children may have difficulty walking the distances required within their local communities, with 6MWD ranging from 110-710 metres (*Burns et al., 2009a*). Slower gait speed is a potential barrier to participation and the ability to keep up with TD peers in school and community environments. There are no published minimally clinically important differences (MCID) values for gait speed in children, however, in older adults MCID range from 0.05 m/sec to 0.13 m/sec (*Perera et al., 2006*). The mean speeds of the CMT cohorts are 0.10 – 0.30 m/sec slower than the TD cohorts or TD reference group (*Lythgo et al., 2009*). This exceeds the adult MCID threshold, suggesting slower walking speeds may impact daily life of children and adolescents with CMT.

In other populations with gait dysfunction researchers have developed functional gait classification systems or scales to more accurately describe functional ambulation in broader environmental contexts. The Functional Mobility Scale (FMS) (*Graham et al., 2004*) is one example commonly used for children with cerebral palsy. The FMS assesses mobility over 5, 50 and 500 metres taking into consideration the different environmental contexts of home, school and community. The FMS also accounts for uneven surfaces and stairs. No such functional

ambulatory assessment has been reported in the CMT pediatric gait literature but consideration of these factors is equally important to this population, with appropriate selection of responsive tools needed.

It is noteworthy that there were no studies of children walking in footwear identified in this review. Whilst assessment of barefoot gait is usual in laboratory settings and provides insight into primary biomechanical dysfunction, this does not readily translate to “real world” function of walking in school and community settings. Children and adolescents with CMT rarely walk barefoot beyond the indoor home environment, typically wearing footwear outdoors. Studies in TD children demonstrate faster gait with a longer stride length when wearing shoes compared to barefoot gait (*Lythgo et al., 2009; Wegener et al., 2011*). Importantly, some people with CMT wear foot orthotics for support of foot and ankle weakness and/or biomechanical alignment. Further studies are needed to understand gait in the functional context of footwear, either with or without orthotics, to more closely reflect school and community function.

A number of limitations warrant consideration in this review. Relatively few studies, small cohort numbers and the lack of statistical analysis in nearly half of the studies limit the findings. Speed-matching in two articles alters interpretation of the spatio-temporal data (*Ferrarin et al., 2012; Ferrarin et al., 2013*). Studies varied in quality in terms of control of extraneous or confounding factors, and uncertain sample generalisability. Of additional note, no study reported the presence of hip dysplasia, which has a reported incidence of up to 8.1% in CMT (*Walker et al., 1994*) and may significantly influence gait.

This systematic review of cross-sectional studies provided limited insight into progression of CMT over time, or the influence of age. It is noteworthy that only a single small study examined longitudinal changes in gait during childhood (*Ferrarin et al., 2013*), finding a small non-significant decline over an 18 month period. In comparison, several studies span adulthood, some of which include adolescents (*Berciano et al., 2006; Shy et al., 2008; Verhamme et al., 2009; Milhe De Bovis et al., 2014; Pelayo-Negro et al., 2014*). As CMT typically emerges during childhood, and is known to be progressive more longitudinal pediatric studies are needed. Future research should include gait assessment in footwear and usual orthotics, in conjunction with evaluations of gait in a functional environmental context to provide important insights into real-life performance of children and adolescents with CMT.

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Conflict of interest statement

The authors have no conflicts of interest.

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Figure legend

Figure 1 Search history and selection flow diagram.

Figure 2 Average gait speed from selected CMT studies in relation to typically developing controls.

Table legend

Table 1 Characteristics of included articles.

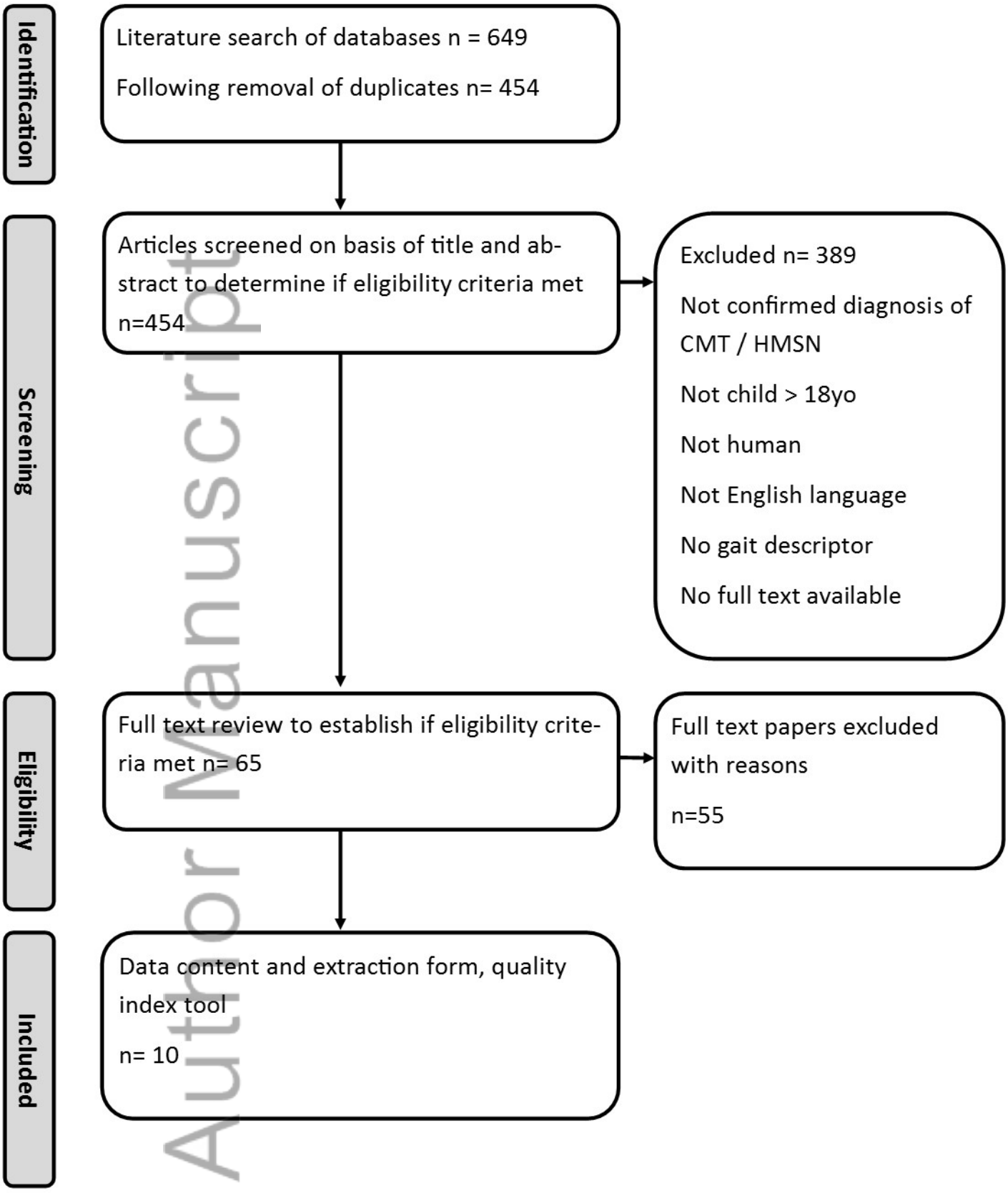
Table 2 Spatio-temporal gait data from included articles reported as mean [SD].

Table 3 Key statistical analysis of lower limb kinematic and kinetic gait data of children with CMT relative to typically developing children.

Supplementary table legend

Supplementary table 1: Example of search strategy.

Supplementary table 2: Quality Index scores.



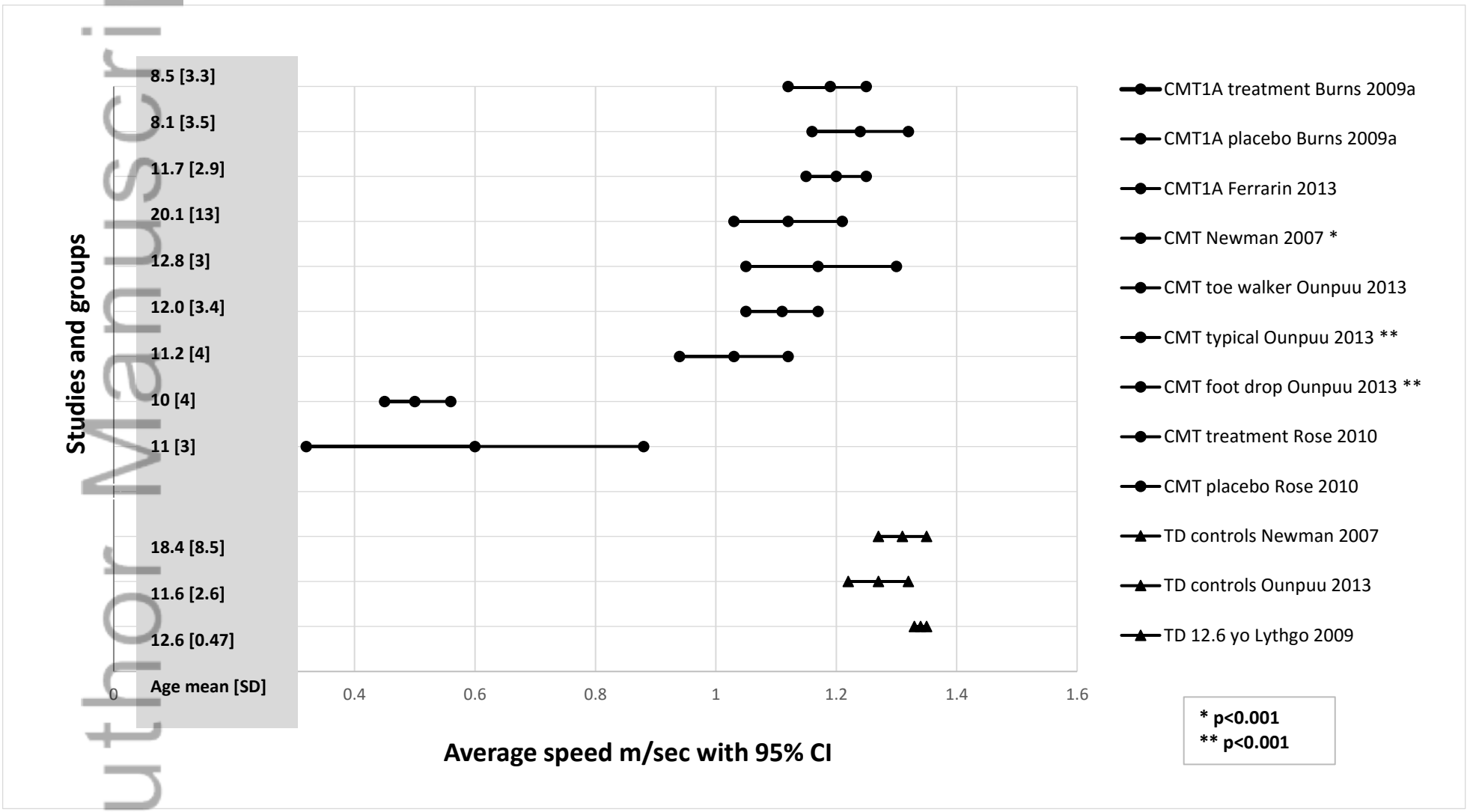


Figure 2 Average gait speed from selected CMT studies in relation to typically developing controls.

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Payment for manuscript preparation	☒	☐	☐			Del ×
						Add +
Patents (planned, pending or issued)	☒	☐	☐			Del ×
						Add +
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						Add +
Payment for development of educational presentations including service on speakers' bureaus	☒	☐	☐			Del ×
						Add +
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						Add +
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						Add +
Other (err on the side of full disclosure)	☒	☐	☐			Del ×
						Add +

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Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

☒ No other relationships/conditions/circumstances that present potential conflict of interest

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

Section 5. Information about relevant nonfinancial associations.

Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

☒ No relevant nonfinancial relationships/conditions/circumstances to report.

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