Published in final edited form as:
J Peripher Nerv Syst. 2011 September ; 16(3): 237–242. doi:10.1111/j.1529-8027.2011.00357.x.

Outcome measures for Charcot-Marie-Tooth disease: clinical and neurofunctional assessment in children

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Abstract

Charcot-Marie-Tooth (CMT) disease is the most common inherited neuromuscular disorder, presenting with symptoms often occurring since childhood, and showing a progressive course. At present, there are no valid and reliable measures for evaluation of impairment and disability in the pediatric population. The aim of this study was to determine the usefulness of outcome measures, commonly used in adult patients, in CMT children. We report the results of a comprehensive evaluation of 21 children affected with CMT type 1A, including clinical examinations, measure of hand and foot muscle strength with a hand-held dynamometer, and the following scales: CMT Neuropathy Score or its clinical component CMT Examination Score, Overall Neuropathy Limitations Scale (ONLS), Walk-12 questionnaire, and nine-hole peg test (9-HPT). Hand grip, three-point pinch, and foot dorsiflexion strength were significantly lower than age/sex equivalent in almost all cases. 9-HPT was significantly abnormal in 62% of patients and CMT Examination Score was <10 points in all cases. ONLS showed presence of minor disability in the upper limbs in 57% and mild abnormalities of gait in 71% of patients. Overall, these scales demonstrated limited potential to measure disability and severity of the disease confirming that it is necessary to identify specific scales for children with CMT.

Keywords

Charcot-Marie-Tooth disease; childhood; disability; impairment; outcome measures

Introduction

Charcot-Marie-Tooth disease type 1A (CMT1A), a dominantly inherited demyelinating polyneuropathy, is the most common hereditary neuropathy, accounting for one-half of all CMT cases *(*Pareyson and Marchesi, 2009*)*. It is characterized by distal limb muscle wasting and weakness, foot deformities, reduced or absent deep tendon reflexes (DTRs), and

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frequent distal sensory loss. The typical average phenotype is relatively benign as compared with other CMT types, but the disease severity is highly variable, and it may run a progressive disabling course. It is reported that CMT1A usually appears during infancy or adolescence (Marques et al., 2005), but few studies have fully investigated the presenting symptoms and clinical features in early childhood (Berciano et al., 2003). In addition, only recently some reports have focused on the clinical and functional involvement of lower and upper limbs in children and adolescents with CMT1A (Burns et al., 2008; 2009).

Specific methodologies to assess impairment, disability, and quality of life have not yet been fully defined in overall CMT patients (Padua et al., 2008; Solari et al., 2008; Reilly et al., 2010), and standardized measures for evaluation of the pediatric CMT population are still completely lacking (Burns et al., 2010). The identification and validation of outcome measures specific for pediatric age appear crucial for the study of the natural history of early onset CMT and for a proper design and conduction of therapeutic trials in children. The aim of this exploratory study was therefore to test if a series of several outcome measures, previously validated for adult patients, prove useful in a cohort of children with CMT1A.

Materials and Methods

Twenty-one children carrying the duplication of peripheral myelin protein-22 gene (*PMP22*) from 16 families were examined. There were 12 males and 9 females; 16 cases were familial, including 4 pairs of siblings, and 5 were sporadic. Age at examination ranged from 6 to 17 years (mean age 11.9±2.8 years). The study was approved by the local ethics committee and informed consent was obtained from the parents of the children.

Clinical and neurological data

A detailed clinical history was collected from the parents about development of motor milestones, presence of foot deformities, fatigue, abnormalities of gait or difficulties in manipulating objects, and age when they noted first symptoms.

A comprehensive neurological examination was performed. The presence of pes cavus was assessed using the fifth component of foot posture index (FPI) that evaluates the congruence of the medial longitudinal arch of the foot (Burns et al., 2009). All patients underwent a standardized protocol that included the following evaluations:

- Videorecording of gait on frontal and sagittal plane according to a standard protocol (Toro et al., 2003). Children were asked to walk at their natural speed; they were also asked to walk on heels and tiptoes.
- CMTNS scale (Shy et al., 2005): for the 12 children in whom neurophysiological data were not available, we calculated the clinical component CMT Examination Score (CMTES).
- Overall Neuropathy Limitations Scale (ONLS) (Graham and Hughes, 2006a): due to the young age of some of the patients and the lack of validation of ONLS in the pediatric population, we decided to administer and videorecord the items from the checklist using the same scoring system (from 0 = no limitations to 5 or 7 = no purposeful movement, for the upper and lower limb section).
- Hand and foot strength: quantitative muscle testing for hand grip, three-point pinch, and foot dorsiflexion were assessed using hand-held dynamometry (C.I.T. Technics, Haren, The Netherlands) according to a standardized procedure (Beenakker et al., 2001).

- The Rolyan nine-hole peg test (9-HPT) (Poole et al., 2005): each hand was tested and the time taken to insert and remove all nine pegs was recorded (in seconds). The time was compared with age-equivalent normative data.
- Walk-12 questionnaire (Graham and Hughes, 2006b): it consists of 12 items that were answered by children from five possible options (1–5). The final score is calculated by subtracting the minimal score possible (12) from the total score and calculating it as a percentage. A higher score indicates a greater limitation in perceived walking ability.

Statistical analysis

9-HPT completion times and dynamometry results were calculated as z scores. The z score indicates the deviation from the mean population score (which is set at zero), stratified by gender and age, and permits direct comparisons between different tests within and between subjects. A z score $|>2|$, that is, lying outside 95% of the normal distribution, is conventionally considered abnormal.

The correlation test was used to evaluate the relationship between age at onset of the first symptoms and all the different neurofunctional measures. The Shapiro-Wilk test for normality was performed. The Pearson correlation test was used for normally distributed variables; the non-parametric Spearman correlation test was performed to assess the remaining variables.

Results

Clinical and neurological data

Clinical data and results of the standardized evaluations are reported in Fig. 1 and Table 1.

Motor development was normal in all children but one, who achieved independent walking at the age of 24 months. The age at onset of the first symptoms was variable (Table 1), ranging from 12 months to 11 years (median age 3 years); only one child, referred to us as he was the brother of another patient, was asymptomatic at the first observation. Early clinical symptoms reported by the parents in the remaining 20 children were the following: fatigue, frequent falls and clumsiness in standing up from the floor, in walking, running, or climbing stairs in 12 children (57%); foot deformities (pes planus or cavus) in 6 children (29%); and abnormalities of gait with toe walking in 2 children (10%). The appearance of foot deformities and abnormal gait were associated in two children. No difficulties in manipulation or other symptoms involving the upper limbs were reported as early clinical manifestations.

Neurological examination revealed absence of DTRs in lower limbs in all cases and heel walking impairment in 20/21 patients (95%), pes cavus was present in 16/21 (76%) with values of the fifth subtest of FPI as −1 in nine cases and −2 in seven cases, tremor in 8/21 (38%), tiptoes walking difficulties in 6/21 (29%), touch/pain hypoesthesia in 5/21 (24%), vibratory hypoesthesia in 3/21 (14%), and scoliosis in 2/21 (9%). Foot finger abnormalities (hammer toes and/or clawing of the toes) were observed in 6/21 patients (28%), all aging more than 12 years (Fig. 1).

Videorecording of gait

The analysis of gait showed the following results: reduced foot dorsiflexion during the swing phase with foot drop during the initial foot contact subphase in 7/21 patients (33%) and flat-foot landing during the loading response with foot drop and reduced or absent propulsion during the push-off subphase in 6/21 patients (29%). Gait was normal in 8/21

patients (38%); 4 of these 8 subjects, however, showed an abnormal load distribution during the mid-stance phase on the external board of the foot, while another child showed recurvatum of the knee during the mid-stance phase. Walking on the heels was difficult in almost all cases, and tiptoe walking was difficult in about one-third of patients, who were all older than 12 years.

CMT Examination Score–CMT Neuropathy Score

CMTES was assessed in all patients. Neurophysiological data were obtained in 9 children for whom we could calculate the CMTNS, while in the remaining 12 we were not able to collect scores on motor and sensory nerve conduction studies as genetic testing had already confirmed diagnosis and parents refused further electrophysiological investigations. CMTES was <10 points in all the patients, and CMTNS ranged from 2 to 10 in the nine children with recorded data on nerve conduction (Table 1). The scores were maximally abnormal in the parameters “strength of legs” and “strength of arms,” and minimally abnormal in the parameters “pin sensibility” and “vibration.”

Overall Neuropathy Limitations Scale

Minor symptoms in the upper limbs, mainly difficulty in doing or undoing buttons or zips, were observed in 12/21 patients (score = 0 in 9 cases, 1 in 11 cases, and 2 in 1 case). Mild abnormalities of gait without any functional limitation in walking, climbing stairs, and running were found in 15/21 patients (score = 0 in 6 cases and 2 in 15 cases; Table 1).

Hand and foot strength

Strength values for foot dorsiflexion and hand grip were significantly lower (z score <2 SD) than age/sex-equivalent data in all the 21 patients and in 14 cases (67%), respectively. Three-point pinch strength was significantly lower (z score <2 SD) than age/sex-equivalent data in 20/21 patients (95%); the remaining patients showed a z score between −1 and −2 SD (Table 1).

Nine-hole peg test

Mean completion time for the whole sample was 24.0 s (SD 3.81, range 10.7–30.4). Higher completion times (z score >2 SD) than normative data were observed in 13/21 patients (62%; Table 1).

Walk-12

Running, balance, long-distance walking, long-standing, walking, climbing, and descending stairs were the activities reported to be mainly involved. No difficulties were reported for two children. Scores <33% were reported in the remaining 19 (Table 1).

Correlation results

9-HPT completion times positively correlated with ONLS upper limb and total scores (ρ = 0.639, p = 0.002 and r = 0.586, p = 0.005, respectively) with CMTNS and CMTES (r = 0.697, p = 0.037 and ρ = 0.617, p = 0.003, respectively). CMTES also positively correlated with Walk-12 questionnaire (ρ = 0.476, p = 0.029) and ONLS upper limb and total scores (ρ = 0.548, p = 0.010 and ρ = 0.515, p = 0.017, respectively). Hand grip negatively correlated with age (r = −0.653, p = 0.001). No correlation was found between age at onset of the first symptoms and the different neurofunctional measures.

Discussion

The aims of this study were to evaluate a pediatric population with CMT1A collecting data on the first symptoms and their age at onset, and to verify the usefulness of the outcome measures commonly used in adult patients.

In agreement with previous studies reporting onset of first symptoms before school age (Berciano et al., 2003), we found that in about half of the cases the parents noticed the first signs of the disease within the age of 3 years. Fatigue, frequent falls, and clumsiness were the early clinical symptoms reported by parents in more than half of cases, while foot deformities (pes planus or cavus) were noted in about one-third as first evidence of the disease. These findings confirm that initial symptoms can be quite subtle and variable in young patients with CMT1A; thus, a comprehensive neurological assessment of children with a positive family history of the disease is highly recommended.

At neurological evaluation, loss of DTRs in lower limbs was a constant sign, while sensory loss was less frequent; these data are in keeping with other authors reporting that motor function in children is affected to a greater extent than sensory function (Berciano et al., 2003; Marques et al., 2005). Scoliosis was observed in 9% of the cases in our series and is consistent with the onset of this sign in the first decade of life (Marques et al., 2005). Foot deformities were quite frequent in our cohort, with pes cavus observed in a high proportion of patients (76%) and hammer toes and/or clawing of the toes in about one-third of cases, all older than 12 years. Heel walking difficulty was a frequent sign observed in 95% of our cases. These findings are in line with other studies on foot manifestations in children with CMT1A (Berciano et al., 2003; Burns et al., 2009; Haberlova and Seeman, 2010) and they have been recently reported as the most significant independent predictor of poor walking ability in children with CMT1A (Burns et al., 2009). Moreover, it was suggested that imbalance of the foot and ankle musculature plays a role in the development of pes cavus deformity (Rose et al., 2009), strongly highlighting the importance of specifically targeting intervention to strengthen dorsiflexion in the affected children to prevent contracture, deformity, and long-term disability.

The analysis of gait further confirms that walking abnormalities are quite frequent in young patients with CMT1A. In our cohort, only 36% of cases showed a normal gait, the remaining exhibiting either a reduced dorsiflexion during the swing phase, with foot drop during the initial foot contact subphase, or a flat-foot landing during the loading response, with foot drop and reduced or absent propulsion during the push-off subphase. These findings are supported by preliminary results of instrumented gait analysis and subsequent cluster analysis of the same population (Ferrarin et al., 2011) which identified three different clusters: (1) pseudo-normal patients, not significantly different from controls, (2) patients showing only foot drop, and (3) patients with foot-drop and push-off deficit.

Our data on CMTNS and CMTES are in line with a recent report on the application of these scales in young patients with CMT1A (Haberlova and Seeman, 2010). In our cohort of patients, the scores were always <10 points falling in the range of mild impairment and disability (Shy et al., 2005) and showed no abnormality at all in some parameters. Moreover, these scales are not always easy to perform in children younger than 6 years, in particular for sensation items, due to incomplete collaboration. However, we found a positive correlation between CMTNS and CMTES and the involvement of upper limb function and manual dexterity, investigated by means of the 9-HPT. These findings seem to confirm a possible role of the CMTNS and CMTES scales in the evaluation of impairment and disability in children with CMT1A.

Although some positive correlations with other neurofunctional measures such as 9-HPT and CMTES were observed, the results obtained with ONLS in our case series demonstrate that this instrument is not sensitive enough to detect disability in young children because of poor variability of the scores at this age. On the other hand, the use of the hand-held dynamometer led us to demonstrate that foot dorsiflexion strength was lower than age-equivalent norms in all the patients, confirming the usefulness of this device in quantifying foot and ankle changes in CMT children *(*Burns et al., 2009*)*. Foot dorsiflexion revealed notable progression in a recent 2-year trial with ascorbic acid in CMT1A as it showed a mean worsening of >10% *(*Pareyson et al., 2011*)*. Thus, it may prove to be an important outcome measure as it is also clinically relevant.

Moreover, the evaluation with hand-held dynamometer showed that hand grip and three-point pinch were significantly lower than normative data in the majority of patients (67% and 95%, respectively). We also observed a significant reduction of hand grip strength with age. Similar findings were reported by Burns et al. (2008) who found that fist and pinch grip values were considerably lower than those collected in healthy children aged 5–16 years, and worsened with age.

It is of interest that about 60% of the children showed 9-HPT completion times significantly higher than their peers and that these data were correlated with difficulties in other abilities of the upper limbs. These findings are in keeping with recent studies reporting that hands are often affected within the first years of life in children with CMT1A, although this is often not recognized until the second decade or adulthood *(*Burns et al., 2008*)*, and suggest that the 9-HPT could be a useful and sensitive outcome measure. These results highlight that more attention should be paid to the assessment of hand strength and function in children with CMT1A to address early intervention and prevent long-term disability.

We found a positive correlation between data from Walk-12 questionnaire and data from CMTES as index of clinical disability and functional limitation, although most of the children showed a mild perception of disability. It is of note that the highest scores on Walk-12 questionnaire were obtained from children older than 12 years: the progression of the symptoms and the increasing awareness of the disease may explain these findings.

In conclusion, our study provides further insight on the clinical and neurofunctional features of pediatric patients with CMT1A. Taking together our observations in this cohort of patients, it appears that the standardized scales commonly used in adult patients, with the possible exception of the hand-held dynamometer in selected muscle groups, CMTNS/CMTES, and 9-HPT, are not sensitive enough to detect impairment and disability in children. We suggest that they are not able to capture the mild involvement frequently present at a very early stage of the disease, confirming the need to develop outcome measures that adequately assess the items that are relevant to a child's daily life activities, and that could be also used during the follow-up at older age. Further studies during a follow-up period in the same series of children are in progress to define the responsiveness over time of the outcome measures that we found to be most useful.

Finally, additional studies on wider cohorts *(*Reilly et al., 2010*)* have been recently prompted with the aim to develop and validate specific novel CMT pediatric scales and they could possibly better elucidate the natural history of the disease in the pediatric population with CMT.

Acknowledgments

This study was partially supported by a grant from the Italian Ministry of Health (Ricerca Finalizzata RFFCG-2007-666049) and a grant from Telethon-UILDM Foundation (GUP 10010).

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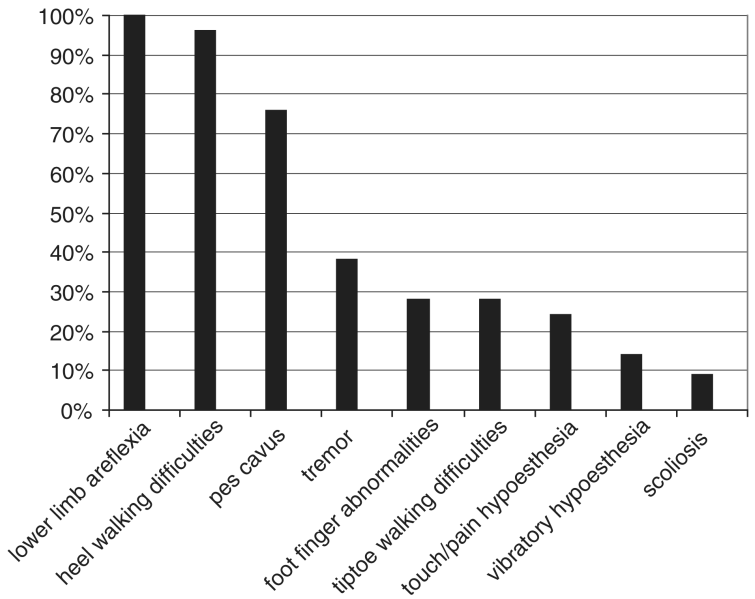

Figure 1. Neurological findings: frequency of clinical signs at first examination.

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Table 1
Clinical data and results of neurofunctional measures.

Case number	Age (years)	Age at onset of first symptoms	CMTES (CMTNS)	ONLS Upper/lower limbs	Hand grip z score (N)	Three-point pinch z score (N)	Foot dorsiflexion z score (N)	9-HPT z score (s)	Walk-12 (%
1	6	20 months	4	1/2	−1.2 (40)	−2.5 (17)	−3.9 (28)	+3.6 (30.81)	
2	8	3 years	1	0/2	−1.7 (58)	−4.6 (12)	−6.5 (11)	+0.73 (20.09)	
3	9	4 years	4 (6)	0/2	−3.6 (60)	−1.9 (30)	−3.9 (12)	+2.62 (23.68)	
4	9	7 years	4	1/0	−1.8 (76)	−4.8 (15)	−4.1 (15)	+2.7 (30.43)	
5	10	3 years	2 (5)	0/2	−0.8 (86)	−3 (18)	−5.1 (22)	+2.24 (24.34)	
6	10	8 years	1 (6)	0/2	−0.6 (92)	−2.4 (28)	−5.3 (19)	+1.45 (21.65)	
7	10	12 months	2	1/0	−2.3 (94)	−3.7 (22)	−7.4 (20)	+0.68 (21.71)	
8	12	3 years	8	2/2	−2.2 (64)	−5 (14)	−4.8 (12)	+5.8 (27.66)	
9	12	5 years	9	1/2	−2.1 (68)	−5.2 (14)	−4.7 (18)	+6.46 (28.73)	
10	12	Asymptomatic	4	1/0	−0.9 (166)	−2 (40)	−5 (31)	+1.20 (21.02)	
11	12	3 years	7 (10)	1/2	−2.9 (34)	−5.6 (10)	−4.8 (12)	+5.02 (26.47)	
12	13	3 years	2 (3)	0/0	−1.8 (134)	−3.1 (19)	−3.5 (27)	+1.48 (21.72)	
13	14	2 years	4 (6)	1/0	−2.7 (132)	−5.6 (17)	−3.9 (24)	+3.04 (27.22)	
14	14	11 years	5 (8)	0/2	−3.2 (96)	−4.6 (35)	−4.2 (3)	+1.02 (20.78)	
15	14	6 years	2	0/2	−2.4 (148)	−4.3 (40)	−4 (18)	−0.08 (17.78)	
16	14	10 years	8	1/2	−2.9 (118)	−5.2 (24)	−4.1 (12)	+2.38 (24.43)	
17	15	3 years	3	1/2	−2.9 (152)	−2.9 (43)	−5.1 (10)	+3.8 (28.41)	
18	15	4 years	2 (2)	0/2	−2.7 (174)	−4.6 (21)	−4.6 (34)	+0.39 (17.75)	
19	16	18 months	4	1/2	−3.9 (184)	−3.6 (60)	−4.7 (9)	+3.85 (22.82)	
20	16	2 years	2	1/0	−4.0 (180)	−5.4 (22)	−4.5 (23)	+3.35 (23.53)	
21	17	6 years	4 (6)	0/2	−3.5 (214)	−3.7 (58)	−4.2 (36)	+3.05 (23.00)	

CMTES, Charcot-Marie-Tooth Examination Score; CMTNS, Charcot-Marie-Tooth Neuropathy Score; 9-HPT, nine-hole peg test; N, Newton; ONLS, Overall Neuropathy Limitations Scale.