ELSEVIER

Utility of Charcot-Marie-Tooth Neuropathy Score in Children With Type 1A Disease

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The aim of this study was to evaluate the utility of the Charcot-Marie-Tooth Neuropathy Score (CMTNS) for evaluation of disease severity in young children with Charcot-Marie-Tooth type 1A. Current validated scoring scales for Charcot-Marie-Tooth are the CMTNS and the Neuropathy Impairment Score (NIS). Both work well for adult patients, and usually also for children over 10 years of age. There is no validation of scales for young children. Children with genetically proven Charcot-Marie-Tooth type 1A disease ($n = 20$, aged 3 to 10 years) were examined clinically, followed by electrophysiologic examination, and were scored under the CMTNS scale. The clinical symptoms were mild; the two most frequent symptoms were difficulty in heel walking and lower limb areflexia. The score was maximally abnormal in four of the nine categories. Categories for sensation, sensory symptoms, and motor symptoms of the arms were normal in all cases. The score was below 8 for all tested children. To conclude, the CMTNS in children aged 10 years and younger has limited sensitivity; out of nine categories, only four are useful. Thus, evaluation of disease severity and progression in young children with Charcot-Marie-Tooth disease remains limited, and there is need for other, effective scoring systems.

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Introduction

Charcot-Marie-Tooth disease, which is the most common hereditary peripheral neuropathy, is clinically characterized by progressive weakness and atrophy of distal muscles of the limbs [1]. Its incidence is up to 1 in 2500 people [2]. Charcot-Marie-Tooth type 1A is by far the most frequent form, accounting for 60-70% of all Charcot-Marie-Tooth patients [3,4]. This disorder is most frequently caused by a duplication of a 1.5-Mb region of the peripheral myelin protein 22 gene (*PMP22*) on the short arm of chromosome 17 [5,6]. As yet there is no cure for Charcot-Marie-Tooth type 1A, although some animal tests and clinical trials are under way [7,8]. To learn more about Charcot-Marie-Tooth disease, methods are needed to measure the natural history and response to particular therapy. The Charcot-Marie-Tooth Neuropathy Score (CMTNS) scale (Table 1) was recently validated to measure the disability and impairment of all types of Charcot-Marie-Tooth patients [9-12]. The scale was evaluated only on adults.

Symptoms of Charcot-Marie-Tooth type 1A typically begin during the first two decades, and there is a need for evaluation of the disability in the early beginning of the disease. Neither the CMTNS nor any other scale has yet been tested or validated on a cohort of young children (age $\leq$10 years) with Charcot-Marie-Tooth type 1A disease. The aim of the present study was, therefore, to evaluate the usefulness of the CMTNS in a cohort of children with the Charcot-Marie-Tooth type 1A duplication, age 10 years and younger.

Patients and Methods

Twenty children carrying the Charcot-Marie-Tooth type 1A duplication from 18 unrelated Charcot-Marie-Tooth type 1A families were examined and monitored. Six of the cases were sporadic; the other 14 were familial. Sixteen of the patients were boys, and four were girls. Age at examination ranged from 3 to 10 years (mean, 7 years). The children were clinically evaluated by taking a detailed history from their parents and performing a comprehensive neurologic and electrophysiologic examination. The

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Table 1. Charcot-Marie-Tooth Neuropathy Score (CMTNS) scale

Parameter	Score				
	0	1	2	3	4
Sensory symptoms	None	Limited to toes	Extended up to and may include ankle	Extended up to and may include knee	Extended above knee
Motor symptoms arms	None	Trips, catches toes, slaps feet	AFO on at least 1 leg or ankle support	Cane, walker, ankle surgery	Wheelchair most of the time
Motor symptoms legs	None	Reduced in fingers/toes	Unable to do buttons or zippers but can write	Cannot write or use keyboard	Proximal arms
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to and may include wrist/ankle	Reduced up to and may include elbow/knee	Reduced above elbow/knee
Vibration	Normal	Reduced at fingers/toes	Reduced at wrist/ankle	Reduced at elbow/knee	Reduced above elbow/knee
Strength of legs	Normal	4+, 4, or 4− on foot dorsiflexion	≤ Foot dorsiflexion	≤ Dorsiflexion and plantar flexion	Proximal weakness
Strength of arms	Normal	4+,4, or 4− on intrinsics or finger extensor	≤ Intrinsics or finger extensors	≤ Wrist extensors	Weak above elbow
Ulnar CMAP (Median)	>6 mV (>4 mV)	4.0-5.9 mV (2.8-3.9)	2.0-3.9 mV (1.2-2.7)	0.1-1.9 mV (0.1-1.1)	Absent (Absent)
Ulnar SNAP (Median)	>9 μV (>22 μV)	6.0-8.9 μV (14-21.9)	3.0-5.9 μV (7-13.9 μV)	0.1-2.9 μV (0.1-6.9)	Absent (Absent)

The maximum total score is 36.

Abbreviations:
AFO = Ankle-foot orthosis
CMAP = Compound muscle action potential
SNAP = Sensory nerve action potential

parents were specifically questioned about the onset of the first symptoms, progression, complicating factors (e.g., infections, antibiotic therapy, vaccination), rehabilitation therapy, and orthopedic treatment or use of any walking aid.

The examination included testing for muscle weakness and atrophy of arms (especially the hand intrinsic muscles) and legs (especially the foot muscles, including atrophy of the extensor digitorum brevis muscle) [13]. Objective assessment of muscle strength was based on the Medical Research Council (MRC) grading system. Patients were evaluated for foot deformities (including pes cavus, planus, varus, and valgus), difficulties in heel walking (measured in centimeters from the ground to the edge of the fifth digit, with a threshold limit for abnormality of <3 cm), shortening of the Achilles tendons (limit for abnormality, <10°), tremor, and scoliosis.

All patients had nerve conduction study of one motor and one sensory nerve in the upper limb and all were scored on the CMTNS scale. For the nerve conduction study, standard techniques were used, with percutaneous stimulation; for sensory nerve conduction velocity, antidromic testing was used. Temperature during testing was rigorously controlled at >32°C. All patients were evaluated by the same investigator.

The parents were appropriately informed about this study and consented to all examinations. The study was approved by the local ethics committee.

Results

Most of the evaluated data from all patients are shown in Table 2. The first symptom as reported by parents in all symptomatic patients (18/20) was clumsiness in walking, which was less in running, occurring before the age of 4 years, and typically since attainment of independent walking, about the age of 1.5 years. All patients had normal motor and mental development, and all patients were able to walk independently before the age of 1.5 year. Two patients (aged 3 and 7 years) were still asymptomatic, according to their parents.

The progression of disability slowly continues; except for time, no complicating factor has been found.

Most of the symptomatic patients used multivitamins and had regular rehabilitation. One had surgical prolongation of Achilles tendons at the age of 10 years. None of the patients used a walking aid, apart from orthopedic shoes.

In clinical evaluation, two signs occurred most frequently. The first was difficulty in heel walking, present in 17/20 patients (85%), and including the children reported as asymptomatic by their parents. Ten patients (50%) were not able to walk on their heels at all. Eight of the 17 patients with difficulty in heel walking had shortened Achilles tendons. The second most common sign was hypo- or areflexia in lower limbs, which was seen in 16/20 patients (80%).

Four patients (20%) had atrophy of small foot muscles. Atrophy of the extensor digitorum brevis muscle was observed in 3/20 patients (15%) and was never severe; the muscle atrophy appeared in patients older than 6 years of age. Seven of the 20 patients (35%) had distal muscle weakness; in all cases it was mild weakness in dorsiflexion of the toes (MRC 4). Other muscular weakness or atrophy was not observed.

Eighteen patients (90%) had foot deformity. Ten patients (50%) had deformity type pes cavus. All of the patients with pes cavus were older than 6 years of age. Eight patients (40%) had pes planus or planovalgus; age in this group ranged from 3 to 8 years.

Table 2. Clinical data for 20 young children with genetically proven Charcot-Marie-Tooth type 1A disease

Age, Yr/Sex	Positive Family History	Difficulty in Heel Walking	Deformities in Foot	Strength in Foot (0-5)	Atrophy in Intrinsic Muscles	Atrophy of m.EDB	Reflexes in Legs	Contractures of Achilles tendon	Score on CMTNS
3/M	yes	yes	planus	normal	no	no	present	no	4
3/F	yes	yes	not present	normal	no	no	present	no	6
3/F	yes	yes	planovalgus	normal	no	no	areflexia	no	3
4/M	yes	yes	planovalgus	normal	no	no	areflexia	no	4
5/M	yes	no	planus	normal	no	no	present	no	4
5/F	no	yes	planus	normal	no	no	areflexia	yes	5
6/M	yes	no	cavus	normal	yes	yes	present	no	7
6/M	yes	yes	cavus	normal	yes	no	present	yes	6
7/M	yes	yes	cavus	normal	no	no	areflexia	yes	7
7/M	no	no	planovalgus	normal	yes	yes	areflexia	no	6
7/M	yes	yes	not present	normal	no	yes	areflexia	no	7
7/M	yes	yes	planovalgus	normal	no	no	areflexia	no	4
7/M	no	yes	cavus	DF4	no	no	areflexia	yes	8
7/M	no	yes	cavus	DF4	no	no	areflexia	yes	5
8/M	yes	yes	cavus	DF 4	no	no	areflexia	yes	7
8/M	yes	yes	planus	DF4	yes	yes	present	yes	3
9/M	yes	yes	cavus	DF 4	no	no	areflexia	no	7
9/M	no	yes	cavus	DF4	no	no	areflexia	no	7
10/M	yes	yes	cavus	DF 4	no	no	areflexia	yes	8
10/F	no	yes	cavus	normal	no	no	present	no	7

Abbreviations:
CMTNS = Charcot-Marie-Tooth Neuropathy Score
DF = Dorsiflexion
m.EDB = Extensor digitorum brevis muscle

Six of the 20 patients (30%) had no detectable sensory nerve action potential of one of the sensory nerves in the arms. The age of these six patients ranged from 6 to 10 years. Compound muscle action potential in arms was detected in all patients.

The CMTNS score was less than 10 points in all patients, with a maximum of 8, minimum of 3, and mean of 5.35 points (Table 3). According to the classification [9], therefore, all were in the range of mildly affected patients. The CMTNS scores were maximally abnormal in only four of the nine parameters. There were no abnormalities in sensory symptoms, strength in arms, vibration in arms and legs, pin sensibility, and motor symptoms in arms (Table 3). The most points were achieved in electromyographic abnormalities, especially in sensory nerve action potentials.

Discussion

Difficulty in heel walking was the earliest and one of the two most common and consistent signs of Charcot-Marie-Tooth type 1A disease and it appeared even in otherwise asymptomatic children. In most of the patients, difficulty in heel walking was accompanied by foot deformities consisting of a variable combination of pes cavus, planus, or planovalgus; in some patients, difficulty in heel walking appeared without objective evidence of any muscular atrophy or shortening of Achilles tendons. These data correspond to previous observations [13,14] and support the theory that the foot deformity (due to intrinsic muscle atrophy of the foot) and difficulty in heel walking start before the patient becomes aware of any symptoms—and in some cases even before any clinical possibility of visually recognizing the early intrinsic foot muscle atrophy.

The second most frequent sign of Charcot-Marie-Tooth type 1A disease was areflexia of lower limbs. In the present series, there was one 3-year-old girl who already had areflexia and two older symptomatic children (5 and 8 years of age) with normal reflexes. There were no clear correlations between areflexia and age and severity of disease.

The CMTNS scale was originally evaluated and validated for both Charcot-Marie-Tooth type 1 and type 2, and it was validated only on adult patients [9]. In the present series of young children (age $\leq$10 years) with Charcot-Marie-Tooth type 1A, the CMTNS score was always below 10 points, falling in the range of mild disability [9]. Children in the present series exhibited no abnormality at all on five parameters out of the nine in the CMTNS scale. Most of the abnormalities were identified in electrophysiologic examination; in terms of clinical symptoms, there were abnormalities only in type of walking and, in fewer cases, in leg strength. These findings limit the use of the CMTNS scale in evaluating disease severity in Charcot-Marie-Tooth type 1A for young children (age $\leq$10 years) and highlight the need for other effective scoring systems for young Charcot-Marie-Tooth children.

The primary limitations of the present study are the small size of the cohort of patients and the absence of follow-up monitoring. Our observations should be extended over

Table 3. Score on the Charcot-Marie-Tooth Neuropathy Score (CMTNS) scale in 20 young children with genetically proven type 1A disease

CMTNS Parameter	Score		
	Max	Mean	Min
Sensory symptoms	0	0	0
Strength in arms	0	0	0
Vibration sense in arms and legs	0	0	0
Pin sensibility	0	0	0
Motor symptoms in arms	0	0	0
Motor symptoms in legs	1	0.85	0
Strength in legs	1	0.35	0
Compound muscle action potential	2	1.7	1
Sensory nerve action potential	4	2.85	1
Total score	8	5.35	3

time and need to be confirmed on a larger cohort of young children with Charcot-Marie-Tooth type 1A disease.

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