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Feasibility, Validity, and Reliability of the Virtual CMT Infant Toddler Scale (vCMTInfS): A Remote Evaluation of Infants/Toddlers With CMT

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ABSTRACT

Background and Aims: The CMT Infant Scale (CMTInfS) enables evaluation of infants/toddlers in clinic. Our aim was to evaluate the feasibility, reliability, and validity of a virtual version of the CMTInfS (vCMTInfS).

Methods: Children aged 55 months or less were evaluated either in clinic using CMTInfS or remotely via telemedicine using the vCMTInfS. A trained clinical evaluator remotely directed activities with assistance from the parent/caregiver. vCMTInfS scores were calculated using the CMTInfS calculator available at www.ClinicalOutcomeMeasures.org. Clinical evaluators also used the Brazelton Neonatal Behavior assessment scale to give insight into the behavior of the child during the exam.

Results: Twenty children (10 males and 10 females) aged 6–55 months with confirmed or at risk for CMT were evaluated. The mean in person (IP) CMT Infant and Toddler Scale (CMTInfS) raw score (4.11, SD = 2.76) was not significantly different from the mean initial virtual (V1) CMTInfS raw score (3.78, SD = 2.59) using a two-tailed test ($t = 1.000$, $p = 0.347$). Differences between the first and second (V2) visits as well as between the IP and V2 visits were also nonsignificant.

Interpretation: Our data demonstrate that children aged 55 months or less can be effectively evaluated remotely using the vCMTInfS, which will expand the number of very young children who can be evaluated with rare forms of CMT.

1 | Introduction

Charcot–Marie–Tooth disease (CMT) refers to inherited peripheral neuropathies that are not part of a larger syndrome. CMT affects 1:2500 individuals [1] and can be divided into several groups—dominantly inherited demyelinating (CMT1), dominantly inherited axonal (CMT2), X-linked (CMTX) and recessively inherited neuropathies; the latter can be further separated into demyelinating (CMT4) and axonal (AR-CMT2) forms. These groups are then subdivided according to the causal genes. Mutations in >140 genes cause CMT. Most CMT patients have autosomal dominant inheritance, and CMT1A (caused by a duplication of the *PMP22* gene [2, 3]) is the most common form of CMT, affecting about 1:5000 individuals [4]; CMTX1 (mutations in *GJB1*,1:25000), CMT1B (mutations in *MPZ*,1:36000), and CMT2A (mutations in *MFN2*, 1:36000) are the next three most frequent forms [4]. CMT4C, caused by recessive *SH3TC2* mutations, and CMT-SORD, caused by recessive *SORD* mutations, are the most common recessive demyelinating and axonal forms, respectively, each accounting for < 1% of all CMT cases [4, 5].

Extensive natural history data have been collected on adults with CMT for CMT1A [6], CMT1B [7], CMTX1 [8], CMT2A [9] and CMT4C [10]. Specific clinical outcome assessments (COA) including the CMT Exam Score (CMTES) [11], CMT Functional Outcome Scale (CMT-FOM) [12], and CMT Health Index (CMT-HI) [13] have been developed for adults to enable natural history studies and clinical trials. Thus, clinical trials are underway for CMT-SORD (Applied Therapeutics) or are being developed with Sephin 1 for CMT1B [14, 15], gene replacement for CMTX1 [16] and CMT4C [17], and CRISPR gene editing for CMT2A [18].

However, clinical impairment begins in childhood for most forms of CMT including CMT1A [6], CMT1B [7], CMTX1 [8], CMT2A [9] and CMT4C [10]. Moreover, for both axonal and demyelinating subtypes of CMT, clinical impairment correlates better with axonal degeneration than with demyelination itself [19–23]. It would, therefore, be ideal to ultimately treat these children in early childhood, before extensive axonal degeneration and clinical impairment occur, particularly since the mechanisms of axonal degeneration may be independent of the specific genetic cause of the neuropathy. We have previously developed the CMT Pediatric Scale (CMTPedS), which is a valid, reliable, and sensitive functional scale using normative data from 1000 individuals of different ages [24]. CMTPedS can detect progression over 2 years in children with CMT1A between 4 and 20 years of age [25]. However, CMTPedS is not suitable for evaluation of children less than 3 years of age. For these children, we have developed the CMT Infant Scale (CMTInfS) in order to measure impairment and progression in children less than 4 years of age [26]. Recruitment for CMTInfS has been limited, in part because families with severely impaired infants and toddlers often have difficulty traveling to CMT clinics. Also, parents with mildly impaired or clinically asymptomatic young children may not feel the need to bring their children to clinics for treatment. Accordingly, we have developed a virtual form of the CMTInfS, vCMTInfS, to permit evaluation of young children in their own home, which we present in this manuscript.

2 | Materials and Methods

2.1 | vCMTInfS

The vCMTinfS is identical to the CMTInfS [26] except that it was performed remotely using a Zoom or similar telemedicine format. Children in the study were either subjects seen in the University of Iowa CMT clinic, were children with known CMT, or with a known family history of CMT. After signing informed consent, parents/caregivers were provided with vCMTInfS Equipment and Training Resource Kits made up of items used to perform the CMTInfS during in-person visits (Figure 1). They were also asked to provide a sweater with a one-inch button (2.5 cm) provided by the caregiver. Children seen in the Iowa CMT clinic underwent an initial in-person evaluation with CMTInfS to allow comparison with subsequent remote evaluation scores. All children underwent two virtual evaluations via Zoom telemedicine in the participant's home; the first after approximately 2 weeks from the in-person visit and the second for test–retest assessments approximately 1 month later.

Clinical evaluators contacted parents/caregivers prior to the virtual evaluations to review the protocols and ensure that there

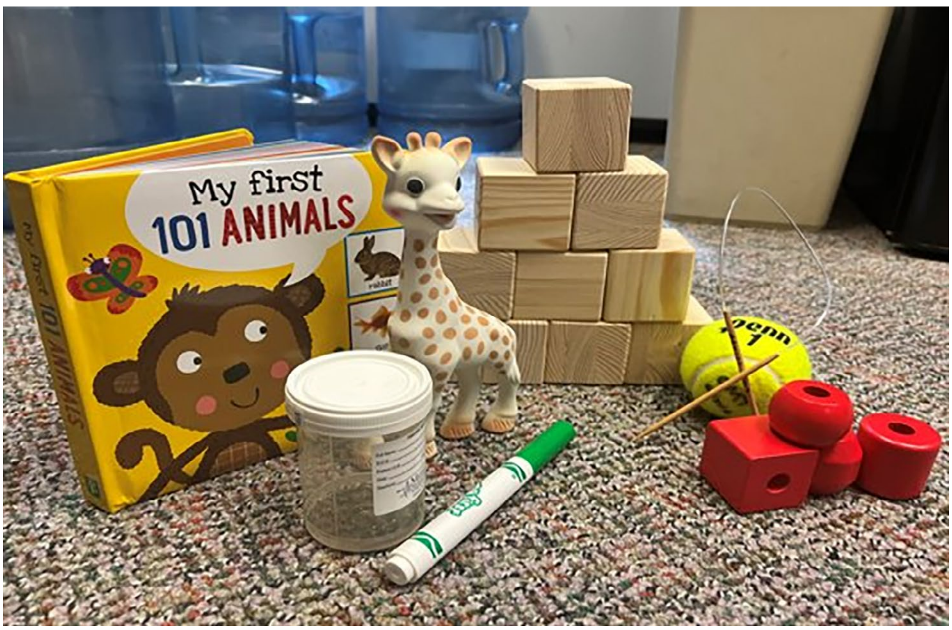

FIGURE 1 | Photo of equipment used during virtual infant exams. These items include a picture book, standard urine collection cup, Sophie the Giraffe, tennis ball, Crayola 8 my first washable marker, blocks ×10, wooden dowls and string, beads. Standard printer paper was also sent in the kits.

was a safe open area in place to perform the evaluations. Having an open area was needed to complete items such as running and throwing a ball without risk of injury. The clinical evaluator then directed the caregiver to perform the various components of the vCMTInfS with the infant, while the clinical evaluator observed the child via Zoom. When necessary, to ensure cooperation by the infant, the clinical evaluator turned off their own camera so that the child could not see them, and asked the caregiver to use headphones so that the child could not hear the clinical evaluator. This was offered to the parent when children's behavior was difficult, but only used once. The clinical evaluator scored the evaluation using the CMTInfS exam sheet [26]. Scores were calculated using the CMTInfS calculator on www.ClinicalOutcomeMeasures.org and both raw and Z-scores were obtained. The Z-score was used to score the impairment level. Clinical evaluators also used the Brazelton Neonatal Behavior assessment scale [27] on the 0–100 mm visual analogue scale (VAS) to give insight into the behavior of the child during the exam and explain unexpected scores.

Equipment kits were made up of items listed in the CMTInfS equipment and training resource kit (Figure 1) that lists items, approximate price, and a picture example. This list includes all the items in the previously published CMTInfS [26]. However, because it proved difficult to obtain the identical beads and wooden dowel used in the original paper, we substituted a 41 cm wooden dowel with string and beads of 2.3–3.5 cm in diameter for this portion of the instrument. All children used this string and beads. We did not note any differences in children's ability to use the string and beads compared to those in our original in-clinic study [26].

3 | Results

3.1 | Demographics

Twenty children (10 males and 10 females), ages 0–4 years (< 55 months) were evaluated; 13 with a confirmed diagnosis and 7 at risk for developing CMT because of a confirmed genetic diagnosis in the family. Three children had CMT1A, two had CMT1B, two had CMT4C, one had CMT2A, one had CMT1E, one had CMTX1, one had CMT4A, one had CMT4B3, and one had CMT1D. At-risk children included three for CMT1A, one for CMT1D, one for CMT2F, and two where the gene had been identified in the family, but the parents did not yet know the type. Nine children completed the in-person (IP) testing and two Virtual exams (V1, V2) while eight completed just V1 and V2. The remaining three children only completed V1. The Demographic data is summarized in Table 1.

3.2 | Distribution of Scores

Scoring was normalized for age and gender using Z-scores, as has been previously described [26]. Total scores can range from 0 to 29, with higher positive scores demonstrating more severe impairment. Z-scores, a measure of the child's ability related to unaffected children of the same age and sex, were necessary to interpret the score in light of the participant's growth and development due to age and sex. In our cohort, Z-scores, a measure of the child's ability related to unaffected children of the same age and sex, ranged from the mildest score of −2.278, which was for a child at risk for CMT2F, to +5.784 for the most severely affected child who had CMT1E. Raw scores ranged from 0 to 29. The distribution of Z-scores and raw scores is shown in Table 2. Scores for five of the participants clearly differed from age- and sex-matched controls. These scores were from children with CMT4B3, CMT1E, CMT2A, CMT1D, and CMT1B. These five children were all 32–48 months old. Fifteen children had scores in or near the normal range [26], such that it was difficult to determine whether they were yet showing signs of CMT. These included all of the children in the at-risk group, including a 19-month boy who scored in the moderate range instead of the mild range for the second virtual exam because he refused to stack six to eight blocks. He had stacked blocks perfectly in his first virtual visit, suggesting that the later problem with blocks was the result of an unwillingness to perform the task rather than a lack of ability to do so. Taken together, these data suggest that most of these infants and toddlers performed activities in the normal range for their age, up to the age of 55 months (Table 3).

3.3 | Validity

A parametric analysis was completed using a paired t-test between children's IP raw scores and their V1 and V2 raw scores. The mean IP raw score (4.11, SD = 2.76) was not significantly different to the mean V1 raw score (3.78, SD = 2.59) using a two tailed test ($t = 1.000$, $p = 0.347$). A second paired sample t-test was completed between children's mean IP raw scores (4.11, SD = 2.76) and their mean V2 raw scores (3.56, SD = 2.96) and this difference was nonsignificant using a two-tailed test ($t = 1.000$, $p = 0.347$). In addition, a correlational analysis showed that children's IP raw scores and virtual raw scores were very similar regardless of testing format (IP to V1, $r = 0.93$, $p < 0.001$; IP to V2, $r = 0.83$, $p = 0.005$).

3.4 | Repeatability

A parametric analysis was completed using a paired t-test between the 17 children's V1 and V2 scores (nine that had IP scores and eight who did not have IP scores) to assess the reliability of the virtual measure over time. There was no significant difference between children's V1 and V2 raw scores ($t = 0.719$, $p = 0.483$ using a two tailed test). Additionally, the correlation between the children's V1 and V2 raw scores was significantly correlated ($r = 0.96$, $p < 0.001$). The results of these tests showed that children's' virtual scores were stable over the time period used in the study. A final reliability assessment was performed on just the V1 and V2 raw scores of all 17 children (nine that had IP scores and eight who did not have IP scores). The correlation between the V1 and V2 raw scores for this sample was also significant ($r = 0.96$, $p < 0.001$), providing additional support for the stability of children's test scores.

3.5 | Role of Behavior

To assess possible effects of behavior on the scoring, we utilized the 100 mm visual analogue scale previously developed for the

TABLE 1 | Demographics.

Infant #	Age (months)	Sex	CMT type	Gene	Variant
1	V1: 39	Male	4B3	SBF1	c.3493_3494dupTA (p. Pro1166ThrfsX5) c.5474_5475delTG (p. Val1825GlyfX27)
2	V1: 35	Male	1A	PMP22	PMP22Duplication
3	V1: 40	Male	1E	PMP22	c.215C>T (p.Ser72Leu)
4	V1: 49[c] V2: 50[c]	Female	1A	PMP22	Duplication of PMP22 (3 copies)
5	V1: 46 V2: 48	Male	1B	MPZ	c.404T>C p.(Ile135Thr)
6	V1: 40 V2: 41	Male	2A	MFN2	c.2219G>C (p.Trp740Ser)
7	V1: 18 V2: 19	Male	CMT[a]	Unknown	Unknown
8	V1: 40 V2: 41	Female	CMT[a]	Unknown	Unknown
9	V1: 29 V2: 30	Male	4A	GDAP1	c.116del (p.Lys39Argfs*5) c.393G>C (p.Leu131Phe)
10	IP: 28 V1: 30 V2: 31	Male	1A[b]	PMP22	Duplication of PMP22 (3 copies)
11	IP: 54[2] V1: 54[2] V2: 55[2]	Female	1B	MPZ	c.639dup (p.Arg214Alafs*21)
12	IP: 32 V1: 32 V2: 33	Female	1D	EGR2	c.1150C>A (p.His384Asn)
13	V1: 6 V2: 7	Female	1D[b]	EGR2	c.1150C>A (p.His384Asn)
14	V1: 12 V2: 13	Female	2F[b]	HSPB1	c.418C>G (p.Arg140Gly)
15	IP: 34 V1: 34 V2: 35	Female	1A[b]	PMP22	Duplication of PMP22 (3 copies)
16	IP: 24 V1: 26 V2: 27	Female	1A	PMP22	Duplication of PMP22 (3 copies)
17	IP: 47 V1: 47 V2: 48	Female	1X	GJB1	c.1281 bp duplication of T
18	IP: 47 V1: 48 V2: 48	Male	1A[b]	PMP22	Duplication of PMP22 (3 copies)
19	IP: 49[c] V1: 50[c] V2: 51[c]	Male	4C	SH3TC2	c.2860 C>T p.R954[a] c.3311 C>T p.All04V
20	IP: 26 V1: 26 V2: 27	Female	4C	SH3TC2	c.2860 C>T p.R954[a] c.3311 C>T p.All04V

[a]CMT type unknown in family.
[b]At-risk for CMT type.
[c]Over 48 months.

TABLE 2 | Results of exam broken down by raw score, *Z*-score, impairment level, and behavior scale.

Infant #	Infant age (months)	Visit #	Raw score	*Z*-score	Impairment level	VAS of behavior (0–100 mm)
1	39	V1	7	3.824	Severe	0
2	35	V1	2	−0.479	Unaffected	17
3	40	V1	10	5.784	Severe	4
4	49	V1	3	−1.209	Unaffected	20
	50	V2	0	−0.752	Unaffected	3
5	46	V1	5	2.56	Severe	5
	48	V2	4	1.86	Moderate	2
6	40	V1	6	3.17	Severe	22
	41	V2	3	1.209	Moderate	15
7	18	V1	9	−2.082	Unaffected	7
	19	V2	10	1.372	Moderate	20
8	40	V1	1	−0.98	Unaffected	3
	41	V2	1	−0.098	Unaffected	7
9	29	V1	4	−0.754	Unaffected	6
	30	V2	5	−0.363	Unaffected	11
10	28	IP	6	0.027	Unaffected	43
	28	V1	5	−0.262	Unaffected	4
	31	V2	4	0.023	Mild	25
11	54	IP	1	−0.098	Unaffected	3
	54	V1	2	0.556	Mild	3
	55	V2	2	0.556	Mild	3
12	32	IP	9	1.276	Moderate	15
	32	V1	8	1.025	Moderate	4
	33	V2	7	0.774	Mild	6
13	6	V1	21	0.014	Mild	6
	7	V2	22	0.301	Mild	5
14	12	V1	13	−2.278	Unaffected	3
	13	V2	14	0.482	Mild	3
15	34	IP	5	0.273	Mild	40
	34	V1	3	−0.228	Unaffected	20
	35	V2	5	0.273	Mild	5
16	24	IP	6	−1.192	Unaffected	7
	26	V1	7	0.418	Mild	3
	27	V2	5	−0.363	Unaffected	5
17	47	IP	2	0.556	Mild	3
	47	V1	1	−0.098	Unaffected	2
	48	V2	1	−0.098	Unaffected	2

(Continues)

TABLE 2 | (Continued)

Infant #	Infant age (months)	Visit #	Raw score	*Z*-score	Impairment level	VAS of behavior (0–100 mm)
18	47	IP	1	−0.098	Unaffected	3
	48	V1	1	−0.098	Unaffected	3
	49	V2	0	−0.752	Unaffected	3
19	49	IP	2	0.556	Mild	16
	50	V1	2	0.556	Mild	7
	51	V2	0	−0.752	Unaffected	0
20	26	IP	5	−0.363	Unaffected	3
	26	V1	5	−0.363	Unaffected	1
	27	V2	8	0.809	Mild	85

in-person CMTInfS [28]. Zero is excellent behavior in performing the study, whereas 100 is the most disruptive behavior, making it difficult to complete and interpret the results. We found that 17 of our 20 children scored less than 25 mm on the scale at all of their visits, suggesting that disruptive behavior was not an issue in their performances. We noted that behavior at home visits was often better than at the in-person visit for those who underwent both. For the remaining three children, behavior was greater than 40 mm on at least one of their assessments. The scores for these three children were still similar at their various visits, although they would on occasion refuse to perform an activity that they had successfully performed previously. In general, performing the evaluation earlier in the day with the child rested improved the behavior, as did minimizing distractions, such as being able to see or hear the clinical evaluator, as opposed to just the caretaker. However, overall vCMTInfS scores were reproducible for all 20 children, as described above, and the behavior scores were similar for in-person and remote evaluations.

4 | Discussion

We have developed the virtual CMTInfS (vCMTInfS) to evaluate infants and toddlers less than 55 months to enable remote evaluation of these young children who might otherwise be unable to attend a CMT clinic where they could be evaluated in person. The vCMTInfS is identical to the in-person CMTInfS except that it is performed remotely, using a Zoom or similar video telemedicine format. A trained clinical evaluator directs a parent or other caregiver on how to perform the various tasks in the instrument while the clinical evaluator observes and scores the vCMTInfS. We found that the vCMTInfS strongly correlated with the in person CMTInfS, gave reproducible results when compared to in person visits, and demonstrated strong test–retest reliability. Taken together, our data demonstrate that the vCMTInfS can serve as a surrogate instrument for infants and toddlers who are unable to be evaluated in person in clinics.

Standardization and safety were important concerns in designing vCMTInfS. We asked that the remote examination be performed in an open area with adequate space, with a small table and chair that the child could easily sit at. To maximize reproducibility with our clinic evaluations, the families were sent a vCMTInfS equipment and training resource kit (Figure 1) with all the same equipment that was used for in-person visits, with the exception of a sweater with a large buttonhole that the families were asked to provide. Caregivers were contacted in advance and trained on how the evaluation would be performed. The clinical evaluators were trained both remotely and in person in the performance of the vCMTInfS.

There were lessons we learned in the performance of vCMTInfS in order to minimize behavioral issues that could limit the accuracy of the evaluation. First, we recognized that adequate intellectual development is necessary to obtain good cooperation, particularly for the younger infants/toddlers. Second, we recognized the need to perform the study at the time that the child was most likely to be alert and cooperative. Typically, this would have been early in the morning after the child had eaten or at a time when the child would have recently awoken from a nap. Third, we quickly learned that seeing and hearing instructions from a person on a computer screen was sometimes distractive for the child. As a result, we turned off the camera on our computers and, when necessary, asked the caregiver to wear headphones so the child would not hear our voices as we directed the caregiver. Finally, if the child was clearly not being cooperative, we learned to reschedule the evaluation. This did not have to be done often; only two exams were rescheduled due to behavior.

We believe that the vCMTInfS has great value for several reasons. First this enables young children to be evaluated for natural history studies when they would not otherwise be able to be seen by trained clinical evaluators. This is particularly important for rare forms of CMT such as recessive disorders that present with delayed motor milestones and where there are currently only small numbers of children available. Natural history studies to enable "clinical trial readiness" are currently underway for a number of very rare inherited neuropathies including giant axonal neuropathy(GAN) [29], CMT4B [30], and CMT4J [31] among many others. vCMTES should permit increased recruitment of children with these rare disorders who would otherwise be unable to be evaluated.

vCMTInfS also should enable investigators to increase the genetic distribution of children evaluated in CMT studies,

TABLE 3 | Results of vCMTInfS virtual evaluations and in-clinic evaluations, showing total raw score, *Z*-score, impairment level, and lists out the 15 individual components of the exam.

Infant #	Visit #	Raw score	*Z*-score	Impairment	Roll to supine to prone	Sit	Crawl	Squat and recover	Stand on 1 ft	Run	Throw ball	Palmar grasp	Build tower	Point	Scribble/imitate line	Tear paper	Unscrew lid	String beads	Button
1	V1	7	3.824	Severe	0	0	0	0	1	1	2	0	0	0	0	2	0	0	1
	V2																		
2	V1	2	−0.479	Unaffected	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
	V2																		
3	V1	10	5.784	Severe	0	0	1	1	2	2	2	0	0	0	0	1	0	0	1
	V2																		
4	V1	3	−1.209	Unaffected	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0
	V2	0	−0.752	Unaffected	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	V1	5	2.56	Severe	0	0	0	0	1	1	0	0	0	0	0	2	0	0	1
	V2	4	1.86	Moderate	0	0	0	0	1	1	0	0	0	0	0	1	0	0	1
6	V1	6	3.17	Severe	0	0	0	1 (R)	1	0	0	0	0	0	0	2	0	1 (R)	1
	V2	3	1.209	Moderate	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1
7	V1	9	−2.082	Unaffected	0	0	0	0	2	1	1	0	0	0	0	2	1	1	1
	V2	10	1.372	Moderate	0	0	0	0	2	1	1	0	1 (R)	0	1	2	0	1	1
8	V1	1	−0.098	Unaffected	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	V2	1	−0.098	Unaffected	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
9	V1	4	−0.754	Unaffected	0	0	0	0	1	0	0	0	0	0	1	0	0	1	1
	V2	5	−0.363	Unaffected	0	0	0	0	1	1	0	0	0	0	0	1	0	1	1
10	IP	6	0.027	Mild	0	0	0	0	1	0	1	0	0	0	0	3	0	0	1
	V1	5	−0.363	Unaffected	0	0	0	0	1	0	0	0	0	0	0	2	0	1	1
	V2	4	0.023	Mild	0	0	0	0	0	0	0	0	1	0	0	1	0	1	1
11	IP	1	−0.098	Unaffected	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	V1	2	0.556	Mild	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
	V2	2	0.556	Mild	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0

(Continues)

TABLE 3 | (Continued)

Infant #	Visit #	Raw score	*Z*-score	Impairment	Roll to supine to prone	Sit	Crawl	Squat and recover	Stand on 1 ft	Run	Throw ball	Palmar grasp	Build tower	Point	Scribble/imitate line	Tear paper	Unscrew lid	String beads	Button
12	IP	9	1.276	Moderate	0	0	0	1	2	2	0	0	0	0	0	2	0	1	1
	V1	8	1.025	Moderate	0	0	0	1	1	2	0	0	0	0	0	2	0	1	1
	V2	7	0.774	Mild	0	0	0	1	1	2	0	0	0	0	0	1	0	1	1
13	V1	21	0.014	Mild	0	0	1	1	2	2	3	0	3	1	2	3	1	1	1
	V2	22	0.301	Mild	0	0	1	1	2	2	3	0	3	1	3	3	1	1	1
14	V1	13	−2.278	Unaffected	0	0	0	0	1	1	2	1	2	0	1	3	0	1	1
	V2	14	0.482	Mild	0	0	0	0	2	1	2	0	2	0	1	3	1	1	1
15	IP	5	0.273	Mild	0	0	0	0	1	0	0	0	0	0	0	2	0	1	1
	V1	3	−0.228	Unaffected	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1
	V2	5	0.273	Mild	0	0	0	0	1	0	0	0	0	0	0	2	0	1	1
16	IP	6	−1.192	Unaffected	0	0	0	0	1	1	0	0	0	0	1	1	0	1	1
	V1	7	0.418	Mild	0	0	0	0	1	1	1	0	0	0	1	1	0	1	1
	V2	5	−0.363	Unaffected	0	0	0	0	1	1	0	0	0	0	0	1	0	1	1
17	IP	2	0.556	Mild	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
	V1	1	−0.098	Unaffected	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	V2	1	−0.098	Unaffected	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
18	IP	1	−0.098	Unaffected	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	V1	1	−0.098	Unaffected	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	V2	0	−0.752	Unaffected	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	IP	2	0.556	Mild	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
	V1	2	0.556	Mild	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
	V2	0	−0.752	Unaffected	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	IP	5	−0.363	Unaffected	0	0	0	0	1	0	1	0	0	0	0	2	0	0	1
	V1	5	−0.363	Unaffected	0	0	0	0	1	0	1	0	0	0	0	1	0	1	1
	V2	8	0.809	Mild	0	0	0	0	1	0	2	0	0	0	0	3 (R)	0	1 (R)	1

which is increasingly concerning. The Inherited Neuropathy Consortium (INC) maintains the largest collection of natural history data of children with CMT, with data on over 8500 participants. However, approximately 90% of the INC participants self-describe themselves as Caucasian/white. Thus, populations of the many non-white populations are not adequately being evaluated. Not only might there be different distributions of CMT subtypes in different populations, but pathogenic variants in one population could be benign in others [32]. vCMTInfS offers the ability to evaluate children in different ethnic or geographical locations without requiring them to travel to clinics. This would require translations of the instrument into different languages, as we are doing with our CMT pediatric quality of life instrument (pCMTQoL) [33].

The vCMTInfS has the potential of identifying disease onset at the earliest time point, which is important for potential therapies to halt disease progression. For example, children with CMT1B [34], CMT2A [9], and CMT4C [10] are frequently severely impaired as toddlers and are often nonambulatory by the time they reach adulthood. Even more slowly progressive disorders such as CMT1A [35] and CMTX1 [8] usually show symptoms in the first decade of life. We expect successful therapies in multiple CMT subtypes will ultimately involve clinical trials in young children prior to the development of more significant axonal degeneration and its associated disability. The vCMTInfS offers the possibility of evaluating CMT in the youngest age groups, enabling interpretation of clinical trials at or prior to their onset of symptoms.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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